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    U1S 1321 C2C

(56) Documents cited
    GB 1058542   US 3480626
    DE 1194422
    Arzneimittel-Forschung, Vol 17, No 6, pages 719-726.
   Arzneimittel-Forschung, Vol 16, No 12, pages 1581-91
    Note: GB 1058542 and DE 1194422 are equivalent;

(58) Field of search
    C2C

(54) **Azoniaspironortropanol esters, processes for the preparation thereof and pharmaceutical compositions containing them**

(57) The present invention provides a process for the preparation of partly novel azoniaspironortropanol esters of the general formula:-
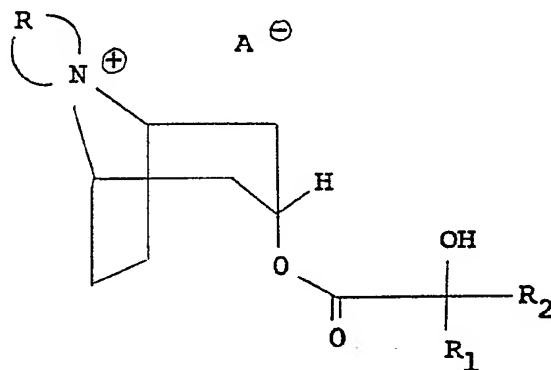
(I)

useful for treating asthma and as broncholytics, are prepared by
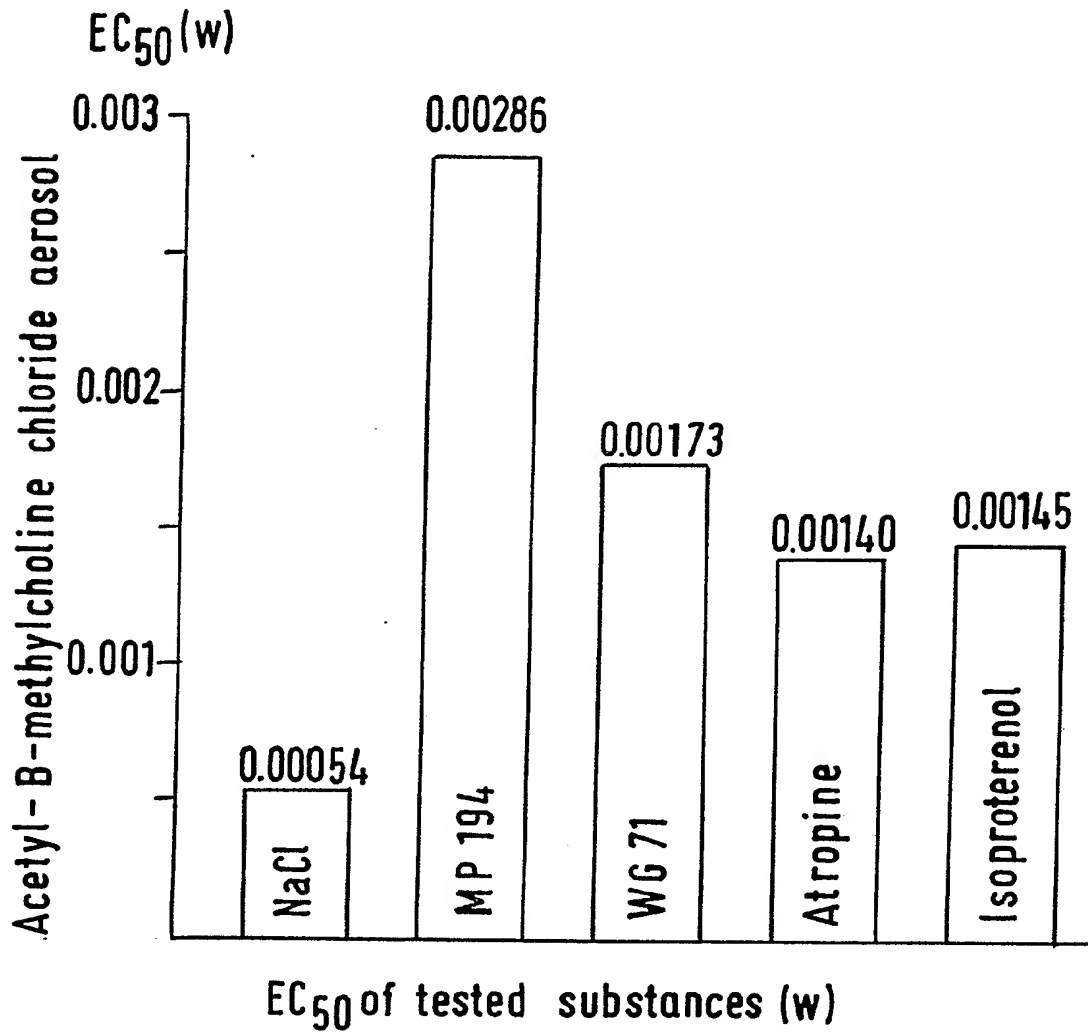   (a) demethylation of tropine to give nortropine,
    (b) reaction of nortropine with a dihalide to give a corresponding azonia compound, and
    (c) esterification of the azonia with an acyl imidazolide compound, using specified conditions in each step.

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Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.
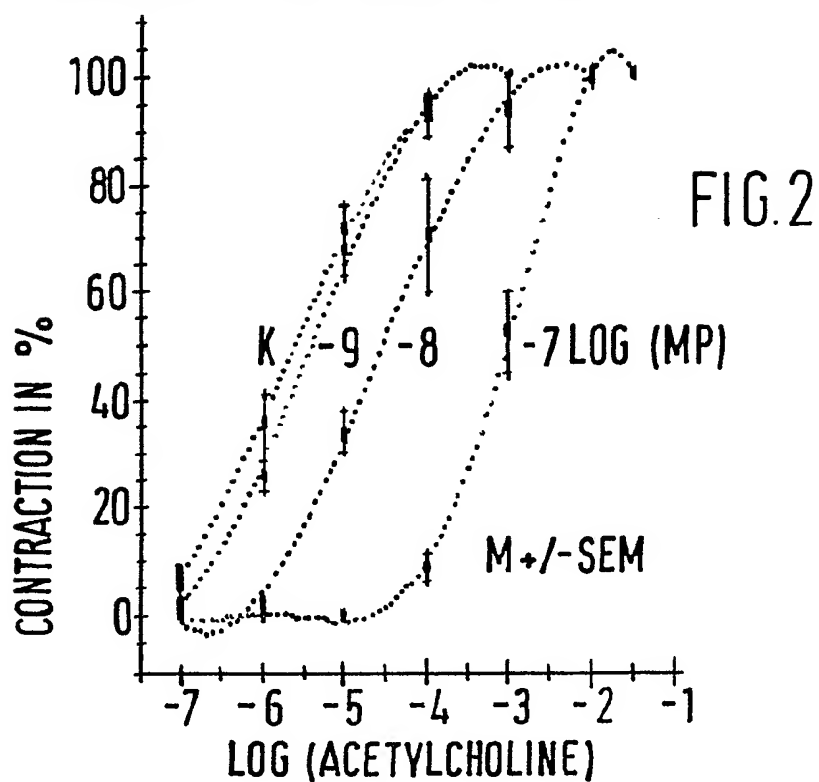
FIG.1

Average effective concentration EC_{50} of the provocation substance 15 minutes after i.p. application of MP 194, WG71, atropine and isoproterenol.
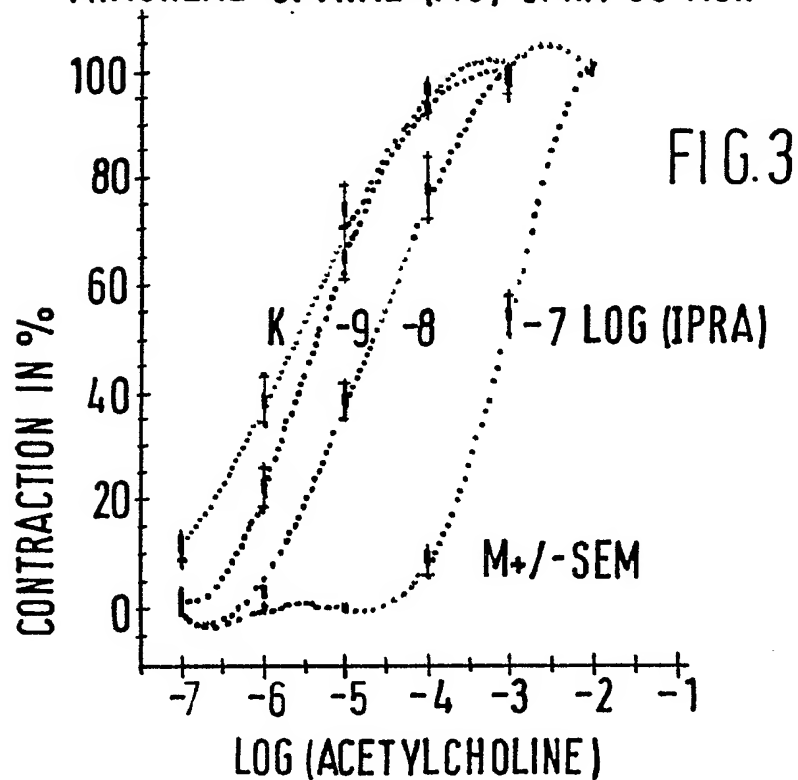

$EC_{50}(w)$

EC50 of tested substances (w)

TRACHEAL SPIRAL (MS): MP194 US ACH

FIG.2

CONTRACTION IN %

K   -9   -8   -7 LOG (MP)

M+/-SEM

LOG (ACETYLCHOLINE)

TRACHEAL SPIRAL (MS) IPRA.US ACH

FIG.3

CONTRACTION IN %

K   -9   -8   -7 LOG (IPRA)

M+/-SEM

LOG (ACETYLCHOLINE)

SPECIFICATION

Azoniaspironortropanol esters, processes for the preparation thereof and pharmaceutical compositions containing them

The present invention is concerned with a process for the preparation of azoniaspironortropanol esters, as well as new azoniaspironortropanol esters and pharmaceutical compositions which contain these compounds.

Because of their excellent spasmolyic properties, azoniaspironortropane derivatives are frequently used pharmaceutically. These compounds are prepared from the naturally occurring tropine but the known processes are laborious and time-consuming and, because of the low yields obtained, are also expensive.

Usually, the preparation of azoniaspironortropane derivatives takes place according to the following reaction scheme:

In the above scheme, R' signifies the residue of a carboxylic acid and A is an amino protective group.

The oxidative demethylation of tropine to give nortropine (step a) is described by S.P. Findley in J.A.C.S.,

75, 3204/1953. However, this process, which takes place with a supersaturated tropine solution at 15°C. and with a reaction time of from 4 to 7 days, cannot be carried out on a technical scale since, under these reaction conditions, the tropine concentration needed for the reaction cannot be kept stable because the tropine precipitates out spontaneously and is thus removed from the further reaction. A homogenisation of the precipitated tropine, for example by an in-line homogeniser, also did not produce any noticeable improvement.

It is also known to carry out the demethylation by exchange of the methyl radical for an N-alkoxycarbonyl radical and subsequent hydrolysis of the alkoxycarbamate (see J.C. Kirn, Org. Prep. Proc. Int., 9, 1-4/1977). In the case of 8-ethoxycarbonylnortropine, the best yield of nortropine to be found in the literature is 16%, referred to tropine (see G. Kraiss and K. Nador, Tetrahedron Letters, 1971, pp. 7-8). Later, it was even reported that an acidic or alkaline splitting of 8-ethoxycarbonylnortropine is not possible (see T.A. Monzka, J.D. Matiskella and R.A. Partyka, Tetrahedron Letters, 1974, pp. 1325-1327).

The preparation of azoniaspironortropane derivatives by quaternisation and esterification or by the reverse reaction sequence is known from Federal Republic of Germany Patent Specification No. 1,194,422 and from Arzneimittelforschung, 17, 714-719/1967 (steps b and c or steps b' and c'). The hydroxyl group of the nortropine or of the corresponding azoniaspiro compound is thereby esterified by reaction with the appropriate acid chlorides, the hydroxyl group of hydroxycarboxylic acids and possibly the NH group of the nortropine thereby having to be protected. A disadvantage of the processes described in these publications is the poor yield, the esterification of the nortropine (step b') and the subsequent reaction with a dihalide (step c') thereby also requiring two further reaction steps. It has long been known to use acid imidazolides as reagents for the esterification of alcohols (see Chem. Ber., 95, 1284-1297/1962). In particular, Federal Republic of Germany Patent Specification No. 2,003,680 describes the reaction of benzilic acid imidazolide with alcohols or thioalcohols which contain a tertiary amino group.

It is an object of the present invention to provide a process for the preparation of azoniaspironortropanol esters which can be carried out on a technical scale and which permits these compounds to be prepared in a simple manner in good yield.

Surprisingly, we have now found that azoniaspironortropanol esters can be prepared in good yield when the demethylation of tropine is carried out in the presence of a C_1-C_3-chloroalkane which contains a trichloromethyl radical. The nortropine thus obtained is alkylated with a dihalide in the presence of an amine and the corresponding azoniaspiro compound is esterified by reaction with an acid imidazolide in the presence of a catalyst.

Thus, according to the present invention, there is provided a process for the preparation of azoniaspironortropanol esters of the general formula:-
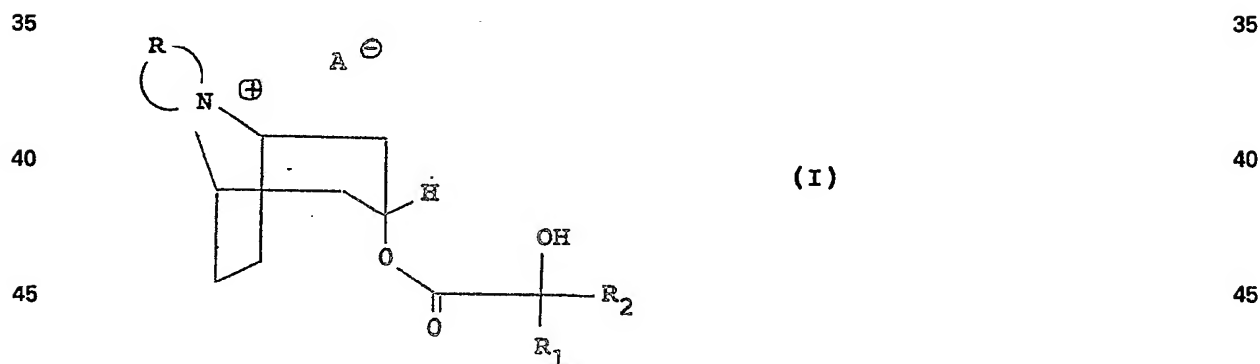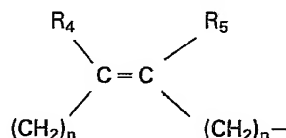

(I)

wherein R signifies one of the following radicals:
   a) an alkylene radical of the general formula:-

$$-(CH_2)_n-CH-(CH_2)_n-$$
(with R_3 on the central CH)
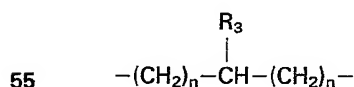
in which R_3 is a hydrogen atom or an alkyl, benzyl, aryl or alkoxy radical and n is a whole number of from 1 to 4,
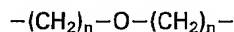   b) an alkenylene radical of the general formula:-

in which R_4 and R_5, which can be the same or different, are hydrogen atoms or alkyl or alkenyl radicals and n is a whole number of from 1 to 4;

   c) an azaalkylene radical of the general formula:-

5

$$-(CH_2)_n-\overset{\overset{\displaystyle R_6}{|}}{N}-(CH_2)_n-$$

in which R_6 is a hydrogen atom or an alkyl, alkoxycarbonyl or acyl radical and n is a whole number of from 2 to

10 4;

   d) an oxaalkylene radical of the general formula:-

$$-(CH_2)_n-O-(CH_2)_n-$$

15 in which n is a whole number of from 2 to 4;

   e) an epoxyalkylene radical of the formula:-

$$-CH_2-\underset{\underset{\displaystyle O}{\diagdown\diagup}}{CH}-CH-CH_2-$$

20

   f) an o-phenylene radical of the general formula:-

25

30

   g) a peri-naphthylene radical of the general formula:-

35

40

or

   h) a 2,3-quinoxalinene radical of the general formula:-

45

50

55

in which, in formulae f) to h), the symbols X and Y, which can be the same or different, are hydrogen atoms or alkyl or alkoxy radicals;

60 and wherein R_1 and R_2, which can be the same or different, are hydrogen or halogen atoms or alkyl, alkoxy, alkoyl, cyclohexyl, phenyl, alkylphenyl, alkoxyphenyl, halophenyl, thienyl or furyl radicals, the alkyl moieties in the said radicals containing up to 6 carbon atoms and being straight-chained or branched, and $A^{\ominus}$ is the anion of a mono- to tribasic mineral acid, by

   a) demethylation of tropine to give nortropine,

65   b) reaction of nortropine with a dihalide to give the corresponding azonia compound and

c) esterification of the azonia compound, wherein
A) the demethylation of tropine of the formula:

5
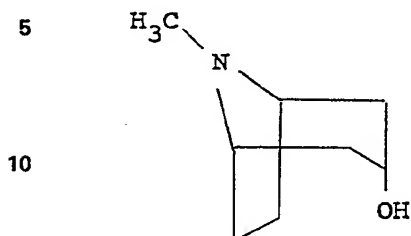
10   (II)

15 is carried out either by working in a C_1-C_3-chloroalkane which contains at least one trichloromethyl radical in
the presence of an oxidation agent in basic aqueous solution or the tropine is reacted with a chloroformic
acid ester in an inert solvent in the presence of an acid-binding agent to give an 8-alkoxycarbonylnortropine
and this is hydrolysed with a base in aqueous solution,
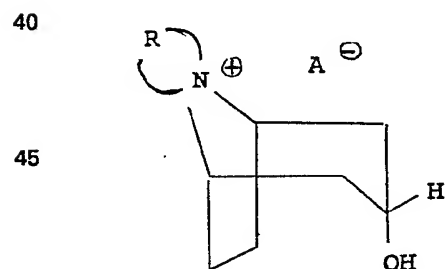   B) the nortropine thus obtained of the formula:-

20
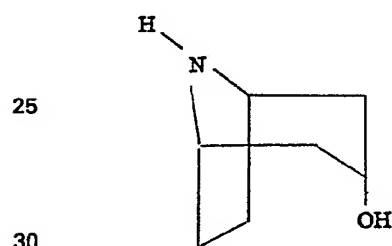
25   (III)

30

is reacted at ambient temperature for 1 or more days in a dipolar aprotic solvent with a compound of the
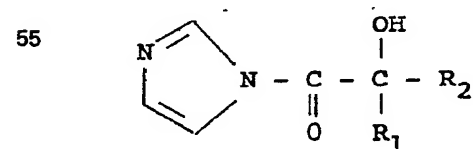general formula:-

35   A – R – A

in which A and R have the above-given meanings, in the presence of a secondary or tertiary amine and
   C) the compound thus obtained of the general formula:-

40

45   (IV)

50

in which R and $A^\ominus$ have the above-given meanings, is esterified in an anhydrous, dipolar, aprotic solvent
with an imidazolide of the general formula:-

55

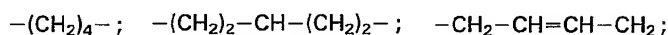   (V)

60

in which R_1 and R_2 have the above-given meanings, in the presence of a catalyst.
   In the above-defined radicals, n can be the same or different, the radicals n preferably being so selected that
there is a 5- or 6-membered ring.
   The anion $A^\ominus$ is preferably a halide ion, such as a chloride, bromide or iodide ion, or a phosphate, sulphate
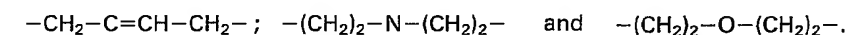65 or nitrate ion.   65

Preferred examples of the radical R include the following:

$$-(CH_2)_4-\;; \quad -(CH_2)_2-\underset{\underset{CH_3}{|}}{CH}-(CH_2)_2-\;; \quad -CH_2-CH=CH-CH_2\;;$$

$$-CH_2-\underset{\underset{\underset{H_3C-C}{\diagdown}{CH_3}}{\diagup CH}}{C}=CH-CH_2-\;; \quad -(CH_2)_2-\underset{\underset{H\;or\;-COCH_3}{|}}{N}-(CH_2)_2- \quad and \quad -(CH_2)_2-O-(CH_2)_2-.$$

Within the scope of the present invention, the alkyl radicals, including those present in alkoxy, acyl, alkylamino and the like radicals, can be straight-chained or branched and contain up to 18 carbon atoms and preferably up to 6 and more preferably up to 4 carbon atoms. Specific examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, hexyl, lauryl and stearyl radicals.

Preferred acyl radicals include the acetyl and benzoyl radicals.

D) When the radical R contains one or more olefinic double bonds in the azonium ring after passing through steps B and/or C, these unsaturated compounds can be hydrogenated in a polar solvent with the help of a noble metal catalyst to give the corresponding saturated compounds, compounds of general formula (I) then being obtained in which R is a radical a) as defined above.

Step A

This process step makes possible the demethylation even on a technical scale and gives nortropine in considerably higher yields in comparison with the prior art. Two process variants can thereby be used, namely, oxidative demethylation or the carbamate method.

The advantages of the oxidative method depend upon the use of a C_1-C_3-chloroalkane containing at least one trichloromethyl radical which is finely dispersed in the aqueous phase. Examples of chloroalkanes which can be used include for example, 1,1,1-trichloroethane, 1,1,1-trichloropropane and preferably chloroform. The amount of chloroalkane used is in the range of from 1 – 10% by volume, preferably from 1 to 5% by volume and most preferably from 2 to 4% by volume.

For the demethylation, there can be employed any oxidation agent normally used for this purpose, potassium ferricyanide being preferred.

The process can be carried out in a wide temperature range, for example of from 0 to 100°C. but it is preferred to work at a temperature of from 20 to 30°C. When the reaction is finished, the product is extracted in counter-current, preferably with the solvent used for the demethylation.

The oxidative method results in a considerable saving of time in comparison with the known methods, which additionally improves the economy of the process according to the present invention.

However, it is preferred to use the carbamate method. For this purpose, tropine is reacted in an inert solvent with a 4 to 6 fold excess of a chloroformic acid ester and generally with ethyl chloroformate. As solvent, there is thereby preferably used a chlorinated hydrocarbon, especially chloroform. The reaction is carried out in the presence of an acid-binding agent, preferably of an alkali metal carbonate or bicarbonate. Working is carried out at an elevated temperature, preferably in the range of from 40 to 80°C.

After substantial distilling off of the solvent, the 8-alkoxycarbonylnortropine thus obtained is hydrolysed with a base in aqueous solution. As base, there is preferably used potassium or sodium hydroxide, preferably in 16 to 20 fold excess.

The nortropine is extracted from the aqueous reaction mixture in the manner described above for the oxidation demethylation.

According to step A, nortropine can be obtained in almost quantitative yield, especially according to the carbamate method.

Step B

The crude nortropine obtained in step A can be used in step B without further purification, in contradistinction to the prior art which requires 48 hours of continuous extraction and crystallisation from diethyl ether. We have, surprisingly, found that the tropine still present in the crude nortropine as impurity is not quaternised under the reaction conditions of step B.

Solvents which can be used for quaternising the nortropine include, for example, N,N-dimethylformamide chloroform or chloroform/acetonitrile. With dihalides in the presence of secondary or tertiary amines, after a reaction period of one or more days at ambient temperature, the corresponding azoniaspiro compounds are obtained in pure form and with high yields. It is preferred to work in anhydrous solution, using nortropine, amine and dihalide in a mole ratio of 1:2:4. As already mentioned, the product obtained in good yield is of

high purity so that a further purification is not necessary.

Secondary amines which can be used for this reaction include, for example, dimethylamine, diethylamine, diisopropylamine, dicyclohexylamine and the like. Examples of tertiary amines which can be used include trimethylamine, triethylamine, pyridine, quinoline and the like. The use of diethylamine is preferred.

Step C

Not only the azoniaspiro compounds obtained from step B but also the carboxylic acid imidazolides are generally of low solubility in the anhydrous, dipolar, aprotic solvents usually employed for such a reaction, for example acetone, acetonitrile, dimethylformamide, tetrahydrofuran and the like. If it is endeavoured to overcome the problems therewith involved by increasing the reaction temperature, then the products resulting therefrom are contaminated with a high proportion of by-products. In particular, carboxylic acid imidazolides which have an unprotected hydroxyl group react with themselves at an elevated temperature.

Surprisingly, we have now found that the reaction of a compound of general formula (IV) with a carboxylic acid imidazolide of general formula (V) can be carried out in the presence of an appropriate catalyst even in the above-mentioned anhydrous, dipolar, aprotic solvents by reacting the reaction components in suspension. The advantage of this process is that the free hydroxyl groups of the carboxylic acid imidazolides do not have to be protected and that the reaction product precipitates from the above-mentioned solvents and, therefore, can be isolated in a simple manner. The reaction product is not, as was to have been expected, contaminated by a reactant introduced into the reaction in solid form.

Furthermore, the reaction takes place under such mild conditions that no fragmentation and elimination reactions attributable to the presence of the quaternary ammonium group take place. Consequently, no corresponding by-products can be formed.

4-(Dimethylamino)-pyridine has proved to be the most advantageous catalyst for this process. This compound can be used in amounts of from 1 to 30 mole % and preferably of from 5 to 10 mole %, referred to the benzilic acid imidazolide.

As solvents, there can be used the above-mentioned anhydrous, dipolar, aprotic solvents. The reaction is carried out at an elevated temperature and preferably at a temperature of from 60 to 80°C.

The preparation of the carboxylic acid imidazolides used in this reaction takes place in known manner by reacting N,N-carbonyldiimidazole with the appropriate carboxylic acids in dry dichloromethane.

Step D

Since, in the case of the quaternisation according to step B) with the dihalides substituted on the double bond, for example with cis-1,4-dichlorobutene, a much greater speed of reaction is achieved, for example from 18 days to 1 hour, it can be advantageous for the preparation of compounds of general formula (I), in which R has the meaning of a radical such as a), for example a benziloyloxynortropane-8-spiro-1'-pyrrolidinium salt, to choose the route via the corresponding unsaturated compounds with subsequent catalytic hydrogenation either after passing through step B) or steps B) and C).
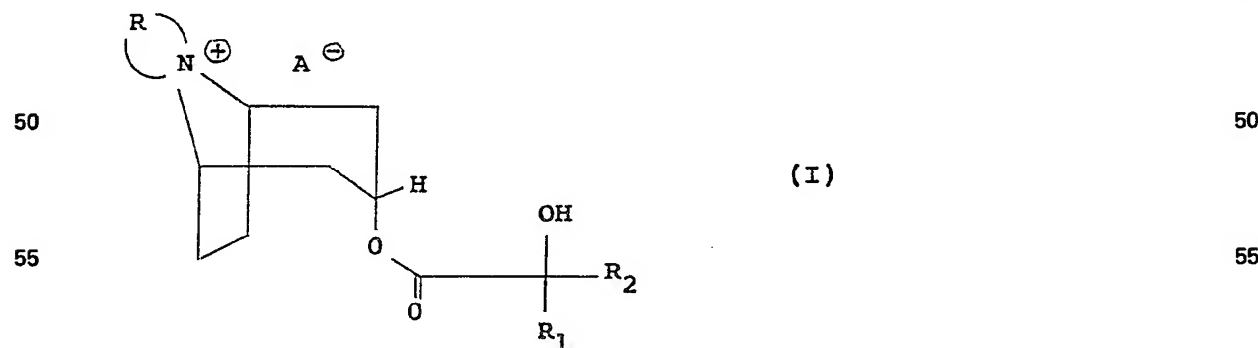
The hydrogenation of the unsaturated compounds is carried out in a polar solvent, such as water or an alcohol containing up to 4 carbon atoms, preferably methanol, in the presence of a noble metal catalyst, such as platinium dioxide or palladium on active charcoal.

In the case of using an unsaturated halide, in carrying out the quaternisation there is used a considerably smaller excess of dihalide. The mole ratio of nortropine, amine and dihalide previously stated to be preferably 1:2:4 in step B) can then be changed to 1:2:2.

The present invention also provides new azoniaspironortropanol esters of the general formula:

(I)

wherein R, R_1, R_2 and $A^\ominus$ have the same meanings as in claim 1, but excluding the following compounds:
azoniaspiro-[3α-phenylglycoloyloxynortropan-8,1'-pyrrolidine] chloride,
azoniaspiro-[3α-diphenylglycoloyloxynortropan-8,1'-pyrrolidine] chloride,
3α-phenylglycoloyloxynortropan-8-spiroisoindolinium chloride,
3α-diphenylglycoloyloxynortropan-8-spiroisoindolinium chloride,
3α-phenylglycoloyloxynortropan-8-spiro-4'-morpholinium chloride,

3α-diphenylglycoloyloxynortropan-8-spiro-4'-morpholinium chloride,
azoniaspiro-[3α-cyclohexylphenylglycoloylnortropan-8,1'-pyrrolidine] chloride,
azoniaspiro-[3α-phenylglycoloyloxynortropan-8,1'-piperidine] chloride and
azoniaspiro-[3α-diphenylglycoloyloxynortropan-8,1'-piperidine] chloride.

5   These compounds possess outstanding spasmolytic properties.   5
      In addition, the present invention provides pharmaceutical compositions containing at least one of the
compounds according to the present invention, optionally in admixture with pharmaceutically-acceptable
carriers and/or adjuvants.
      The following Examples are given for the purpose of illustrating the present invention:-

10   10
Example 1
3α-Benziloyloxynortropane-8-spiro-1'-pyrrolidinium chloride.

Step A
15 *Demethylation of tropine to nortropine*   15
      In a 300 litre stirrer vessel equipped with a reflux condenser, 1.9 kg. tropine (97%, corresponding to 1.843
kg. of pure compound, equal to 13 mole) are dissolved in 240 litres chloroform and 5.7 kg. sodium hydrogen
carbonate powder and 5.3 litres ethyl chloroformate (98%, corresponding to 6.0 kg. and to 55.7 mole) are
stirred in. The reaction mixture is heated to the boil and then heated under reflux for a further 2 hours. The
20 progress of the reaction is monitored by means of thin layer chromatography (silica gel 60;   20
dimethylformamide/diethylamine/ethanol/ethyl acetate 5:10:30:60 v/v/v/v). The reaction mixture is filtered
while hot and the chloroform is distilled off. A solution of 18 kg. 85% potassium hydroxide in 90 litres water is
added to the residue. The reaction mixture is heated to the boil and then heated under reflux for a further 9
hours. The cooled solution is then extracted with chloroform using a Karr column. Extraction conditions: the
25 "stationary" phase is the light phase (aqueous potassium hydroxide solution) which is conveyed at a rate of   25
about 14 litres/hour. The dispersed phase is the heavy chloroform phase which is conveyed at a rate of about
35 to 50 litres/hour. Shaking frequency: 200 strokes/minute; temperature 26 to 28°C.
      In this way, the nortropine formed is extracted from the aqueous potassium hydroxide solution in almost
quantitative yield. After stripping off the solvent, the crude product obtained is used in the following step B)
30 without further purification. There is obtained 1.876 kg. nortropine with a content of 87% (high pressure   30
liquid chromatography: μ-Bondapack C_{18}-column; elution agent: methanol/water 1:9 v/v with PIC-B7). This
corresponds to 1.632 kg. of pure tropine and to a yield of 98%.

Step B
35 *3α-Hydroxynortropane-8-spiro-1'-pyrrolidinium chloride*   35
      The composition of the reaction mixture must be referred to pure nortropine and the mole ratio of
nortropine:diethylamine:1,4-dichlorobutane must be exactly 1:2:4.
      The crude nortropine obtained in step A) (1.186 kg., corresponding to 1.632 kg. of pure substance and to
12.85 mole) is dissolved in 52 litres N,N-dimethylformamide and 2.665 litres (1.876 kg.; 25.7 mole)
40 diethylamine and 5.736 litres (6.528 kg.; 5.14 mole) 1,4-dichlorobutane added thereto. The reaction mixture is 40
left to stand for 18 days at ambient temperature. The crystals which separate out are filtered off with suction,
washed with a little dry acetonitrile and dried at 50°C. in a vacuum drying cabinet. There are obtained 2.25 kg.
(80%, referred to the amount of tropine used in the first step) of pure product; m.p. 250°C.

45 *Step C*   45
3α-Benziloyloxynortropane-8-spiro-1'-pyrrolidinium chloride (trospium chloride)
      a) *Benzilic acid imidazolide*
      1.944 kg. (12 mole) N,N-carbonyldiimidazole are dissolved in 19.2 litres dry dichloromethane with the
exclusion of moisture. 2.736 kg. (12 mole) dry benzilic acid are added thereto, while stirring, at 15 to 20°C. in
50 the course of 6 minutes, whereafter the reaction mixture is stirred for 1 hour at ambient temperature. The   50
benzilic acid thereby first goes into solution but soon afterwards the benzilic acid imidazolide begins to
separate out in solid form. It is filtered off with suction and washed with 0.8 litres dry dichloromethane. There
are obtained 2.4 kg. benzilic acid imidazolide.
      b) *Preparation of the title compound*
55   In a 300 litre stirrer vessel, 1.3 kg. of the compound obtained in step B) are suspended in 230 litres   55
anhydrous acetonitrile and heated to 78°C. A solution of 74.0 g. 4-(dimethylamino)-pyridine in 2 litres
anhydrous acetonitrile is added thereto. A suspension of 2.086 kg. benzilic acid imidazolide in 9.0 litres
anhydrous acetonitrile is then added thereto in three portions at intervals of 30 minutes at 78°C. The reaction
mixture is subsequently stirred at 78°C. until there is achieved a total reaction time of 4 hours after the first
60 addition of benzilic acid imidazolide. The reaction mixture is then cooled to 20°C. and further stirred   60
overnight. The suspension formed is filtered off with suction and washed with some acetonitrile. The
residue, as well as further product obtained by concentration of the mother liquor (total 2.14 kg.), are
recrystallised from isopropanol. There is obtained 1.78 kg. (70%) of pure product; m.p. 258–263°C.
(decomp.).

FD-MS: m/e = 392 (molecule cation)
IR (KBr): γ = 3150, 1735, 1498, 1452, 747.

Example 2

5 *3α-Benziloyloxynortropane-8-spiro-1'-(3'-pyrrolidinium)*   5

Step B
3α-Hydroxynortropane-8-spiro-1'-(3'-pyrrolidinium) chloride
   1.05 ml. (10 mMole) diethylamine and 1.05 ml. (10 mMole) cis-1,4-dichlorobut-2-ene are stirred into a
10 solution of 635 mg. (5 mMole) nortropine in 9.5 ml. N,N-dimethylformamide. After 1 hour, the pure crystalline   10
product is filtered off with suction. The mother liquor is mixed with ethyl acetate until the commencement of
turbidity in order to obtain further product. The crystals are filtered off with suction and washed with a little
acetone. Yield 984 mg. (91% of theory);
m.p. 204°C.
15 FD-MS: m/e = 180 (molecule cation)   15
IR (KBr): γ = 3250, 1621 cm^{-1}.
^{1}H-NMR (90 MHz, D$_2$O, δ-values referred to TSP=0):
   δ = 1.7-2.7 (8H, H-2, H-4, H-6, H-7); 3.92 (2H; H-1, H-5); 4.05 (1H; H-3); 4.14 and 4.31 (each 2H; H-2' and H-5');
5.90 (2H; J-3', H-4').
20   20
Step C
3α-Benziloyloxynortropane-8-spiro-1'-(3'-pyrrolinium) chloride
   530 mg. (2.4 mMole) 3α-hydroxynortropane-8-spiro-1'-(3'-pyrrolinium) chloride are suspended in 353 ml.
anhydrous acetone and stirred in an autoclave for 23 hours at 70°C. with 14 mg. (0.12 mMole)
25 4-dimethylaminopyridine and 678 mg. (2.4 mMole) benzilic acid imidazolide. Upon cooling to ambient   25
temperature, the product crystallises out of the reaction mixture. It is filtered off with suction and washed
with a little acetone. Yield 650 mg. (62% of theory); m.p. 267°C.
FD-MS: m/e = 390 (molecule cation)
IR (KBr): γ = 1722, 1595, 1490, 1445, 741 cm^{-1}.
30 ^{1}H-NMR (90 MHz, D$_2$O, δ-values referred to TSP=0):   30
   δ = 1.3-2.8 (8H; H-2, H-4, H-6, H-7); 3.85 (2H; H-1, H-5); 4.09 and 4.37 (each 2H; H-2' and H-5'); 5.24 (1H; H-3);
5.95 (2H; H-3', H-4'); 7.44 (10H; aromatic protons of the benzilic acid).

Step D
35 *Conversion of 3α-benziloyloxynortropane-8-spiro-1'-(3'-pyrrolinium) chloride into*   35
3α-benziloyloxynortropane-8-spiro-1'-pyrrolidinium chloride
   500 mg. 3α-benziloyloxynortropane-8-spiro-1'-(3'-pyrrolinium) chloride are dissolved in 15 ml. methanol
and, after the addition of a spatula tip of platinum dioxide, hydrogenated at normal pressure and at a
temperature of 25°C. up to the end of the hydrogen take-up. The hydrogenation is carried out in a standard
40 apparatus, such as is illustrated, for example, in Houben-Weyl, Methoden der organischen Chemie, 4th   40
edition, Vol. IV/1c, pub. Georg Thieme Verlag, Stuttgart, New York, 1980, pp. 33-39. After filtering off the
catalyst, the filtrate is evaporated to dryness in a vacuum. According to ^{1}H-NMR spectroscopy, the reaction is
quantitative. Crystallisation is carried out as described in Example 1, Step C.

45 *Example 3*   45
3α-Benziloyloxynortropane-8-spiro-2'-isoindolinium chloride
   1) *3α-Hydroxynortropane-8-spiro-2'-isoindolinium chloride*
   1.27 g. (10 mMole) nortropine are dissolved in 7 ml. chloroform and mixed with 1.46 g. (20 mMole)
diethylamine and 4 g. (40 mMole) 1,2-bis-(chloromethyl)-benzene. The clear reaction solution is left to stand
50 for 24 hours at ambient temperature in a closed vessel. It is then concentrated to one half and mixed with   50
ethyl acetate in order to initiate crystallisation. The crystals are filtered off with suction and recrystallised
from isopropanol/ethyl acetate. Yield 1 g. (38% of theory); m.p. 245−247°C.
FD-MS: m/e = 230 (molecule cation)
IR (KBr): γ = 3168, 757, 742 cm^{-1}.
55 ^{1}H-NMR (250 MHz, D$_2$O, δ-values referred to TSP=0):   55
   δ = 2.09 (2H; H-6a, H-7a); 2.40-2.67 (4H; H-2, H-4); 2.59 (2H; H-6b, H-7b); 4.03 (2H; H-1, H-5); 4.24 (1H; H-3);
4.82 and 4.99 (4H; H-1' and H-3'); 7.47 (4H; H-4' to H-7').
   2) *3α-Benziloyloxynortropane-8-spiro-2'-isoindolinium chloride*
   1.33 g. (5 mMole) 3α-hydroxynortropane-8-spiro-1'-isoindolinium chloride is suspended in 210 ml.
60 anhydrous acetonitrile and heated to 78°C. While stirring, there are first introduced 62 mg. (0.5 mMole)   60
4-dimethylaminopyridine and then, within the course of 2.5 hours, portionwise 3.2 g. (11.5 mMole) benzilic
acid imidazolide. The reaction mixture is further stirred for 5.5 hours at 78°C., then cooled to 22°C. and further
stirred overnight. The solution is concentrated to one quarter of its volume and the product caused to
crystallise by the addition of ethyl acetate. Yield 1.3 g. (54% of theory); m.p. 263-265°C.
65 FD-MS: m/e = 440 (molecule cation).   65

IR (KBr): γ = 1740, 757, 703 cm^{-1}.
^{1}H-NMR (250 MHz, D$_2$O, δ-values referred to TSP=0):

   δ = 1.57 (2H; H-6a, H-7a); 2.03 (2H, H-2a, H-4a); 2.07 (2H; H-6b, H-7b); 2.70 (2H; H-2b, H-4b); 3.86 (2H; H-1,
H-5); 4.69 amd 4.96 (4H; H-1'- and H-3'); 5.32 (1H; H-3); 7.40 – 7.51 (14H; H-4' to H-7' and aromatic protons of
the benzilic acid).

Example 4
3α-Benziloxyoxynortropane-8-spiro-4'-morpholinium chloride
   1) 3α-Hydroxynortropane-8-spiro-4'-morpholinium chloride
   11.8 ml. (113.2 mMole) diethylamine and 26.6 ml. (226.5 mMole) 2,2'-d-chlorodiethyl ether are stirred into a
solution of 7.2 g. (56.6 mMole) nortropine and 70 ml. chloroform. The clear reaction solution is left to stand
for 3 days at ambient temperature in a closed vessel. The oil-crystal mixture which separates out is
homogenised and crystallised through overnight at 0°C. The crystals are filtered off with suction, washed
with a little chloroform and dried under a vacuum at 40°C. for 2 hours. Additional substance is obtained by
evaporating the mother liquor and treating with ethyl acetate. Yield 12.5 g. (95% of theory); m.p. 274 - 276°C.
(decomp.).
FD-MS: m/e = 198 (molecule cation).
IR (KBr): γ = 3320, 892 cm^{-1}.
^{1}N-NMR (250 MHz, D$_2$O, δ-values referred to TSP=0):
   δ = 2.00 (2H; H-6a, H-7a); 2.22-2.62 (6H; H-2, H-4, H-6b, H-7b); 3.50 and 3.65 (4H; H-2' and H-6'); 4.01 and
4.08 (4H; H-2' and H-6'); 4.18 (1H; HO3); 4.22 (2H; H-1 and H-5).
   2) 3α-Benziloxyloxynortropane-8-spiro-4-morpholinium chloride
   7.5 g. (32 mMole) 3α-hydroxynortropane-8-spiro-4'-morpholinium chloride are suspended in 650 ml.
anhydrous acetonitrile and mixed with 0.587 g. (4.8 mMole) 4-(dimethylamino)-pyridine. 26 g. (92.8 mMole)
benzilic acid imidazolide are added portionwise at 79°C. within the course of 3 hours. The reaction mixture is
left to stand for 7 days at ambient temperature and the pure crystalline product is then filtered off with
suction. The crystals obtained are dried under vacuum for 2 hours at 40°C.; yield 8.4 g. (60% of theory); m.p.
225°C. (decomp.).
FD-MS: m/e = 408 (molecule cation).
IR (KBr): γ = 3410, 3183, 1731, 1492, 703 cm^{-1}.
^{1}H-NMR (250 MHz, D$_2$O, δ- values referred to TSP=0):
   δ = 1.51 (2H; H-6a, H-7a); 2.00 (4H; H-2a, H-4a, H-6b, H-7b); 2.63 (2H; H-2b, H-4b); 3.38 and 3.64 (4H; H-2'
and H-6'); 3.99 and 4.04 (4H; H-3' and H-5'); 4.09 (2H; H-1, H-5); 5.30 (1H; H-3); 7.46 (10H; aromatic protons of
the benzilic acid).

Example 5
3α-Benziloxyoxynortropane-8-spiro-1'-pyrrolidino-[3',4'-b]quinoxalinium bromide
   1) 3α-Hydroxynortropan-8-spiro-1'-pyrrolidino-[3',4'-b]quinoxalinium bromide
   4.58 g. (43.6 mMole) diethylamine and 13.85 g. (43.6 mMole) 2,3-bis-(bromoethyl)-quinoxaline are stirred
into a solution of 5.57 g. (43.6 mMole) nortropine and 100 ml. chloroform. The reaction mixture, which has
become warm, is cooled to 20°C., the product thereby precipitating out in crystalline form. It is filtered off with
suction, washed with chloroform and dried in a vacuum for 22 hours at 55°C. Yield 11.1 g. (71% of theory);
m.p. 283°C. (decomp.).
FD-MS: m/e = 282 (molecule cation).
IR (KBr): γ = 3345, 1504, 773 cm^{-1}.
^{1}H-NMR (250 MHz, D$_2$O, δ-values referred to TSP=0):
   δ = 2.21; (2H; H-6a, H-7a); 2.53 – 2.89 (6H; H-2, H-4, H-6b, H-7b); 4.29 (2H; H-1 and H-5); 4.31 (1H; H-3); 5.21
and 5.41 (each 2H; H-2' and H-5'); 7.94 - 8.05 (2H; quinoxaline o-protons); 8.11 - 8.22 (2H; quinoxaline
m-protons).
   2) 3α-Benziloyloxynortropane-8-spiro-1'-pyrrolidino-[3',4'-b]quinoxalinium bromide
   5 g. (1.39 mMole) 3α-hydroxynortropane-8-spiro-1'-pyrrolidino[3',4'-b]-quinoxalinium bromide are
suspended in 130 ml. dried dimethyl sulphoxide and 100 ml. dry acetonitrile. After the addition of 0.26 g. (2.09
mMole) 4-dimethylaminopyridine, the reaction mixture is heated to 78°C. While stirring vigorously, 7.74 g.
(27.8 mMole) benzilic acid imidazolide are added in 3 portions at intervals of 30 minutes. The reaction mixture
is further stirred for 2.5 hours at 78°C and is then cooled to 20°C, and filtered. The filter residue is discarded.
The filtrate is evaporated to dryness at about 0.2 mbar pressure. The residue is extracted with 500 ml. boiling
isopropanol and filtered hot. The filter residue is discarded. The filtrate is concentrated to 200 ml. The product
crystallises out after standing overnight at ambient temperature. It is filtered off with suction, washed with
cold isopropanol and dried in a vacuum for 2 hours at 55°C. Yield 3.5 g. (44% of theory); m.p. 205°C.
(decomp.).
FD-MS: m/e = 492 (molecule cation).
IR (KBr): γ = 3375, 1730, 1504, 763 cm^{-1}.
^{1}H-NMR (250 MHz, CDCl$_3$/CD$_3$OD = 3:1 v/v, δ-values referred to TMS=0):

δ = 1.78 (2H; H-6a, H-7a); 2.08 (2H; H-2a, H-4a); 2.20 (2H; H-6b, H-7b); 2.85 (2H; H-2b, H-4b); 4.23 (2H; H-1, H-5); 4.62 (4H; H-2′, H-5′); 5.35 (1H; H-3); 7.30-7.48 (10H; benzilic acid protons); 7.84-7.97 (2H; quinoxaline o-protons); 8.07-8.22 (2H; quinoxaline m-protons).

5 *Example 6*
3α-Benziloyloxynortropane-8-spiro-2′-(2′-aza-3H-phenolenium) bromide
   1) 1.33 ml. (12.7 mMole) dimethylamine and 4 g. (12.7 mMole) 1,8-bis-(bromoethyl)-naphthalene are stirred into a solution of 1.62 g. (12.7 mMole) nortropine and 75 ml. N,N-dimethylformamide. From the reaction mixture, which has become slightly warm, the product crystallises out within 2 hours. It is filtered off with
10 suction, washed with a little N,N-dimethylformamide and dried in a vacuum at 55°C. for 2 hours. Yield 3.5 g. (76% of theory); m.p. 330°C. (decomp.).
   FD-MS: m/e = 280 (molecule cation):
   IR (KBr): γ = 3410, 1604, 1512 cm⁻¹.
   ¹H-NMR (250 MHz, CDCl₃/CD₃OD = 3:1 v/v, δ-values referred to TMS=0):
15   δ = 2.02 (2H; H-6a, H-7a); 2.39-2.85 (6H; H-2, H-4, H-6b, H-7b); 3.92 (2H; H-1, H-5); 4.28 (1H; H-3); 5.01 and 5.16 (4H; H-1′ and H-3′); 7.51-7.64 (4H; H-5′, H-6′, H-7′, H-8′); 7.93 (2H; H-4′, H-9′).
   2) *3α-Benziloxyoxynortropane-8-spiro-2′-(2′-aza-3H-phenolenium)-bromide*
   2.95 g. (8.2 mMole) 3α-hydroxynortropane-8-spiro-2′-(2′-aza-3H-phenolenium) bromide are suspended in 1660 ml. dry acetonitrile and 160 ml. dry N,N-dimethylformamide. After the addition of 152 mg. (1.2 mMole)
20 4-dimethylaminopyridine, the reaction mixture is heated to 78°C. 4.56 g. (16.4 mMole) benzilic acid imidazolide are added in three portions with vigorous stirring at intervals of 30 minutes. The reaction mixture is then stirred for 2.5 hours at 78°C. and the reaction mixture thereafter evaporated to one half. The precipitated crude product is filtered off with suction at 20°C. and suspended in methanol. The material which is insoluble in methanol is filtered off and discarded. The filtrate is concentrated until the crystallisation of the
25 product commences. After crystallisation overnight at ambient temperature, the product is filtered off with suction and dried in a vacuum for 2 hours at 55°C. Yield 2.1 g. (42% of theory); m.p. 322°C. (decomp.).
   FD-MS: m/e 490 (molecule cation).
   IR (KBr): γ = 3428, 3240, 1738, 1603, 1497 cm⁻¹.
   ¹H-NMR (250 MHz, CDCl₃/CD₃OD = 3:1 v/v, δ-values referred to TMS=0):
30   δ = 1.75 (2H; H-6a, H-7a); 1.94 (2H; H-2a, H-4a); 2.20 (2H; H-6b, H-7b); 2.80 (2H; H-2b, H-4b); 3.85 (2H; H-1, H-5); 4.93 and 5.19 (each 2H; H-1′ and H-3′); 5.45 (1H, H-3); 7.31-7.46 (10H; benzilic acid proton); 7.47-7.67 (4H; H-5′, H-6′, H-7′, H-8′); 7.93 (2H; H.4′, H-9′).

   Example 7
35 *3α-Benziloyloxynortropane-8-spiro-1′-(4′-methyl)-piperidinium chloride*
   1) *3α-Hydroxynortropane-8-spiro-1′-(4′-methyl)-piperidinium chloride*
   7.62 g. (0.06 mole) Nortropine are dissolved in 200 ml. anhydrous N,N-dimethylformamide. After stirring in 8.76 g. (0.12 mole) diethylamine and 37.18 g. (0.24 mole) 1,5-dichloro-3-methylpentane, the reaction mixture is left to stand for 18 days at ambient temperature in a closed vessel. The crystals which separate out are
40 filtered off with suction, washed with a little dry acetonitrile and dried in a vacuum drying cabinet at 50°C. There are obtained 7.84 g. (53% of theory) of pure product; m.p. 290°C. (decomp.).
   FD-MS: m/e = 210 (molecule cation).
   IR (KBr): γ = 3190 cm⁻¹
   ¹H-NMR (250 MHz, D₂O, γ-values in ppm, referred to TSP=0):
45   δ = 1.01 (m; 3H; CH₃); 1.37-2.02 (m; 7H; H-6a, H-7a, H-3′, H-4′, H-5′); 2.20-2.52 (m; 5H; H-2a, H-4a, H-6b, H-7b, OH); 2.60 and 2.67 (2 × t; 2H; H-2b and H-4b); 3.10, 3.20, 3.63 and 3.74 (4 × m; 4H; H-2′ and H-6′); 3.76 and 4.24 (2 × m; 2H; H-1 and H-5); 4.19 (t; 1H; H-3).
   2) *3α-benziloyloxynortropane-8-spiro-1′-(4′-methyl)-piperidinium chloride*
   7.37 g. (30 mMole) 3α-Hydroxynortropane-8-spiro-1′-(4′-methyl)-piperidinium chloride are suspended in
50 650 ml. anhydrous acetonitrile and heated to 78°C., while stirring. At this temperature, there are first stirred in 587 mg. (4.8 mMole) 4-(dimethylamino)pyridine and then, in the course of 2 hours, 13.35 g. (48 mMole) benzilic acid imidazolide in 4 approximately equal portions. Stirring is continued for 1.5 hours at 78°C. and then the reaction mixture is allowed to cool overnight at ambient temperature, without stirring. The crystalline product is filtered off with suction and washed with a little acetone. The crude crystallisate is
55 recrystallised from dry isopropanol. The pure crystals are dried in a vacuum for 2 hours at 40°C. Yield 9.56 g. (70% of theory) as a 1:1 mixed crystallisate with isopropanol; m.p. 256 - 259°C.
   FD-MS: m/e = 420 (molecule cation).
   IR (KBr): γ = 1735 cm⁻¹
   ¹H-NMR (250 MHz, D₂O, δ-values in ppm, referred to TSP=0):
60   δ = 0.98 (m; 3H; CH₃); 1.30-1.65 (m; 4H; H-6a, H-7a, H-3′a, H-5′a); 1.65-2.03 (m; 7H; H-2a, H-4a, H-6b, H-7b, H-3′b, H-4′, H-5′b); 2.52 and 2.72 (m; 2H; H-2b, H-4b); 3.02, 3.19, 3.47, 3.72 (t, t; d; 4H; H-2′ and H-6′); 3.62 and 4.10 (m, m; 2H; H-1 and H-5); 5.30 (t; 1H; H-3); 7.40-7.40 (m; 10H, aromatic protons).

Example 8
3α-(4,4'-Difluorobenziloyloxy)-nortropane-8-spiro-1'-pyrrolidinium chloride

2.17 g. (0.01 mole) 3α-hydroxynortropane-8-spiro-1-pyrrolidinium chloride are dissolved with 2.02 g. (0.01 mole) sodium heptane-1-sulphonate, with warming, in 500 ml. anhydrous acetonitrile. After cooling to 25 to
5   27°C., the sodium chloride precipitate is filtered off with suction with the exclusion of moisture. The solution   5
is mixed with 0.125 g. 4-(dimethylamino)pyridine and transferred to a reaction vessel which is connected to a stirrer vessel in which 4,4'-difluorobenzilic acid imidazolide is prepared. This stirrer vessel is equipped with two dropping funnels. In one dropping funnel, there are placed 2.64 g. (0.01 mole) 4,4'-difluorobenzilic acid (preparation analogous to the description in Federal Republic of Germany Patent Specification No. 20 34
10 943), dissolved in 100 ml. anhydrous acetonitrile. In the other dropping funnel there is placed a solution of   10
2.43 g. (0.015 mole) N,N-carbonyldiimidazole in 150 ml. anhydrous acetonitrile. From each of the two solutions, about one quarter of the volume is run in simultaneously, while stirring, into the stirrer vessel, the mixture is then stirred for 15 minutes and the resultant imidazolide solution transferred, with the strict exclusion of moisture, into the reaction vessel in which the solution of
15 3α-hydroxynortropane-8-spiro-1'-pyrrolidinium heptane-sulphonate is stirred at ambient temperature. This   15
procedure is repeated three times until all the reactants have been combined. The reaction mixture is then boiled under reflux for 2 hours and subsequently cooled overnight to ambient temperature. The reaction mixture is then evaporated to dryness in a rotary evaporator under vacuum. The residue is purified chromatographically over a silica gel column (silica gel 60, 0.063 - 0.200 mm., Merck No. 7734), the mobile
20 phase being 1,2-dichloroethane:acetic acid:methanol: water 57:23:13:7 v/v/v/v). Yield 870 mg. (14% of   20
theory) 3α-(4,4'-difluorobenziloyloxy)-nortropane-8-spiro-1'-pyrrolidinium heptanesulphonate. After passage over a column packed with a strongly basic ion exchanger in the chloride form (Lewatit MP 500), there is obtained the title compound. The crude product is recrystallised from isopropanol, washed with ethyl acetate and dried in a vacuum under vacuum at 40°C. to constant weight. Yield 470 mg. as 1:1 mixed
25 crystallisate with isopropanol;   25
m.p. 242 - 245°C.
FD-MS: m/e = 428 (molecule cation)
IR (KBr): γ = 1508, 1603, 1733 cm^{-1}
^{1}H-NMR (250 MHz, D$_2$O, δ-values in ppm, referred to TSP=0):
30   δ = 1.44-1.67 (m; 2H; H-6a, H-7a); 2.00-2.20 (m; 8H; H-2a, H-4a, H-6b, H-7b, H-3', H-4'); 2.57 and 2.64 (2 × m;   30
2H; H-2b and H-4b); 3.38 and 3.60 (2 × m; 4H; H-2', H-5'); 3.73 (m; 2H; H-1, H-5); 5.27 (t; 1H; H-3); 7.19 and 7.42 (2 × m; 8H; aromatic protons).

Example 9
35 *3α-(4,4'-Dimethylbenziloyloxy)-nortropane-8-spiro-1'-pyrrolidinium chloride*   35
The procedure is as in Example 8 but instead of 4,4'-difluorobenzilic acid there is used 4,4'-dimethylbenzilic acid as starting material (preparation analogous to J.G. Cannon, Org. Chem., 25, 959-962/1960). Yield 1.68 g.; m.p. 175°C.
FD-MS: m/e = 420 (molecule cation)
40 IR (KBr): γ = 1508, 1612 (weak), 1718 cm^{-1} 40
^{1}H-NMR (250 MHz, D$_2$O, δ-values in ppm, referred to TSP=0):
δ = 1.47-1.51 (m; 2H; H-6a, H-7a); 1.79-2.21 (m; 8H; H-2a, H-4a, H-6b, H-7b, H-3', H-4'); 2.33 (s; 6H; 2 × CH$_3$);
2.48-2.66 (m; 2H; H-2b, H-4b); 3.34 and 3.58 (2 × m; 4H; H-2' and H-5'); 3.67 (m; 2H; H-1, H-5); 5.23 (t; 1H; H-3); 7.20-7.31 (m; 8H; aromatic protons).
45   45
Example 10
3α-(4,4'-Di-n-butyloxybenziloyloxy)-nortropane-8-spiro-1'-pyrrolidinium chloride
The procedure is as in Example 8 but instead of 4,4'-difluorobenzilic acid there is used
4,4'-di-n-butyloxybenzilic acid as starting material (preparation analogous to J.G. Cannon, J. Org. Chem. 25,
50 959-962/1960). Yield 240 mg. of crystals which deliquesce at ambient temperature.   50
FD-MS: m/e = 536 (molecule cation)
IR (KBr): γ = 1508, 1580 (weak), 1608, 1734 cm^{-1}
^{1}H-NMR (250 MHz, CDCl$_3$, δ-values in ppm, referred to TSP = 0):
δ = 0.96 (t; 6H; 2 × CH$_3$ of n-butyloxy); 1.47 (t; q; 4H; 2 × CH$_3$ of n-butyloxy); 1.53-1.63 (m; 2H; H-6a, H-7a);
55 1.76 (t, t; 4H; 2 × CH$_3$ of n-butyloxy); 1.80-2.30 (m; 8H; H-2a, H-4a, H-6b, H-7b, H-3', H-4'); 2.62-2.77 (m; 2H;   55
H-2b, H-4b); 3.65 and 3.99 (2 × m; 4H; H-2' and H-5'); 3.94 (t; 4H; 2 × CH$_3$ of n-butyloxy); 4.16 (m; 2H; H-1, H-5); 5.28 (t; 1H; H-3); 6.84 and 7.25 (2 × d; 8H; aromatic protons).

Example 11
60 *3α-(4-n-butyloxybenziloyloxy)-nortropane-8-spiro-1'-pyrrolidinium chloride*   60
The procedure is as in Example 8 but instead of 4,4'-difluorobenzilic acid there is used 4-n-butyloxybenzilic acid as starting material (preparation analogous to C.D. Shacklett and H.A. Smith, J.A.C.S., 75 2654-2657/1953). Yield 250 mg.; m.p. 206°C.
FD-MS: m/e = 464 (molecule cation)
65 IR (KBr): γ = 1512, 1609, 1742 cm^{-1} 65

^{1}H-NMR (250 MHz, CDCl$_3$, δ-values in ppm, referred to TMS=0):
  δ = 0.97 (t; 3H; CH$_3$ of n-butyloxy); 1.50 (t, q; 2H; CH$_2$ of n-butyloxy); 1.56-1.64 (m; 2H; H-6a, H-7a); 1.77 (t,t; 2H; CH$_2$ of n-butyloxy); 1.84-2.45 (m; 8H; H-2a, H-4a, H-6b, H-7b, H-3', H-4'); 2.65-2.85 (m; 2H; H-2b, H-4b); 3.58 and 3.95 (2 × m; 4H; H-2' and H-5'); 3.95 (t; 2H; CH$_2$ of n-butyloxy); 4.08 (m; 2H; H-1 and H-5); 5.30 (t; 1H;
5 6.84 (d) and 7.26-7.37 (m; 9H; aromatic protons).   5

Galenical examples

1. *Tablets*
10   40 mg. azoniaspironortropanol ester according to one of the chemical Examples   10
      20 mg. lactose
      30 mg. starch
      0.5 mg. magnesium stearate
      74.5 mg. microcrystalline cellulose
15   15
2. *Suppositories*
      120 mg. azoniaspironortropanol ester according to one of the chemical Examples
      2 mg. "Aerosil" 200 (silicic acid)
      2278 mg. Witepsol (modified triglycerides of saturated plant fatty acids)
20   20
3. *Solution for intravenous injection*
      20 mg. azoniaspironortropanol ester according to one of the chemical Examples
      4.6 mg. citric acid monohydrate
      14.8 mg. sodium citrate dihydrate ad 2 ml.
25   25
4. *Solution for intravenous infusion*
      500 mg. azoniaspironortropanol ester according to one of the chemical Examples
      130 mg. citric acid monohydrate
      370 mg. sodium citrate dihydrate ad 50 ml.
30   30
5. *Retard form: diffusion pellets*
   Per hard gelatine capsule:

	Without initial dose	With initial dose
sugar spheroids	150 mg.	150 mg.
azoniaspironortropanol ester according to one of the chemical Examples	80 mg.	WS 60 mg.
hydroxypropylcellulose (Klucel)	10 mg.	8 mg.
acrylic or methacrylic esters:		
Endragit RL	2 mg.	2 mg.
Endragit RS	8 mg.	8 mg.
polyethyleneglycol (8000)	1 mg.	1 mg.
talc	5 mg.	5 mg.
		WS 20 mg.
		Klucel 2 mg.

60 6. *Retard form: matrix tablet*   60
      80 mg. azoniaspironortropanol ester according to one of the chemical Examples
      120 mg. lactose
      15 mg. ethyl cellulose
      20 mg. starch
65   2 mg. magnesium stearate   65

3 mg. polyethylene glycol (8000)

7. Retard form: two-layer tablet with initial dose

	1st layer retard tablet	2nd layer retard tablet
azoniaspironortropanol ester	60 mg.	20 mg.
lactose	90 mg.	10 mg.
ethyl cellulose	12 mg.	-
starch	15 mg.	15 mg.
magnesium stearate	1.5 mg.	0.3 mg.
polyethylene glycol (8000)	2 mg.	-
microcrystalline cellulose	-	37.2 mg.

8. Dosed aerosol for inhalation
Formulation per dosage/spray impulse:
0.1 mg. azoniaspironortropanl ester according to one of the chemical Examples
0.02 mg. Span 85 (sorbitan mono- and trifatty acid residue based on oleic acid)
10 μl. Frigen 11 (trichlorofluoromethane)
40 μl. Frigen 12 (dichlorodifluoromethane).

9. Dosed spray for nasal use
Formulation per dosage/spray impulse:
2 mg. azoniaspironortropanol ester according to one of the chemical Examples
90 μl. physiological saline

10. Inhalation solution

trospium chloride	0.100 g.
citric acid monohydrate	0.470 g.
trisodium citrate dihydrate	0.530 g.
sodium chloride	0.645 g.

The solution is prepared by successively dissolving the components in water, followed by sterilising filtration and placing into light-protected containers. The pH value of the solution is about 4.2.

11. Dosed aerosol

trospium chloride	0.030 g.
trichlorofluoromethane/dichloro- difluoromethane	ad 15.0 ml.

The aerosol is prepared by grinding the trospium chloride to a particle size of less than 5 μm., suspending it in cooled and liquefied propellant gas and placing into conventional aerosol containers at about 45 to 50°C. The valve on the container is so chosen that, per spray impulse, 0.1 mg. trospium chloride is applied.
Examples of compounds which can be used according to the present invention include the following:
1. trospium chloride [(3α-benziloyloxynortropane-8-spiro-1'-pyrrolidinium)-chloride]
m.p. 258 - 263°C. (decomp.);
FD-MS: m/e = 392 (molecule cation)
IR (KBr): γ = 3150, 1735, 1498, 1452, 747 cm^{-1}
2. 3α-benziloyloxynortropane-8-spiro-1'-(3'-pyrrolinium) chloride
m.p. 267°C.; FD-MS: m/e = 390 (molecule cation)
IR (KBr): γ = 1722, 1595, 1490, 1445, 741 cm^{-1}
3. 3α-benziloyloxynortropane-8-spiro-2'-isoindolinium chloride
m.p. 263 - 265°C.; FD-MS: m/e = 440 (molecule cation)
IR (KBr): γ = 1740, 757, 745, 703 cm^{-1}

4. 3α-beniloyloxynortropane-8-spiro-4'-morpholinium chloride
m.p. 225°C. (decomp.);
FD-MS: m/e = 408 (molecule cation
IR (KBr): γ = 3410, 3183, 1731, 1492, 703 cm^{-1}
5 5. 3α-benziloyloxynortropane-8-spiro-1'-pyrrolidino-[3',4'-b]quinoxalinium bromide   5
m.p. 205°C. (decomp.);
FD-MS: m/e = 492 (molecule cation)
IR (KBr): γ = 3375, 1730, 1504, 763 cm^{-1}
6. 3α-benziloyloxynortropane-8-spiro-2'-(2'-aza-3H-phenolenium) bromide
10 m.p. 322°C. (decomp.);   10
FD-MS: m/e = 490 (molecule cation)
IR (KBr): γ = 3428, 3240, 1738, 1603, 1497 cm^{-1}.
Experiments were carried out on isolated rat intestine.

15 *Animal material*:   15
Male and female Wistar rats with a body weight of 150 to 250 g. The animals were acclimatised for 1 week at
20 ± 2°C. and at a relative humidity of 50 + 10%. The room illumination was daylight with additional neon
tubes with a day/night illumination rhythm of 7.00 to 18.00 hours. The animals were kept in Makrolon cages
type 4, each being occupied by 10 rats. The cages had a sawdust bedding. The feed was "ssniff" standard
20 feed (Versuchstierdiaten GmbH, 4770 Soest, Germany) available ad libitum and the drinking water, which   20
was tap water from synthetic resin flasks with stainless steel drinking tubes, was available ad libitum.

Substances, dosages:
test substances: compounds of Examples 1 – 6.
25 solvent: demineralised water   25
concentration: 1.185 × 10^{-8} g./ml. bath vessel contents (against Carbachol)
volume administered: 0.25 ml.
time of action before administration of spasmodic:
3 minutes
30 further substances used: carbamoylcholine (Carbochol) hydrochloride, Merck, Darmstadt (Art No. 500 940)   30
sum formula: $C_6H_{15}ClN_2O_2$
concentrations: 4× 10^{-9} g./ml. bath vessel content
2 × 10^{-8} g./ml. bath vessel content
1 × 10^{-7} g./ml. bath vessel content
35   5 × 10^{-7} g./ml. bath vessel content   35
2.5 × 10^{-6} g./ml. bath vessel content
1.25 × 10^{-5} g./ml. bath vessel content
6.25 × 10^{-5} g./ml. bath vessel content
volume administered: 0.25 ml.
40 time of action: 5 minutes   40
Ringer's nutrient solution with the following composition:

sodium chloride = 9.000 g. (E. Merck, Darmstadt)
potassium chloride = 0.210 g. (E. Merck, Darmstadt)
45 sodium bicarbonate = 0.500 g. (E. Merck, Darmstadt)   45
glucose monohydrate = 0.500 g. (E. Merck, Darmstadt)
calcium chloride monohydrate = 0.318 g. (E. Merck, Darmstadt)

Carrying out of the experiments
50   The rats were sacrificed by a neck blow. The abdomen was opened along the median line, an   50
approximately 10 cm. long piece of ileum was removed, immediately transferred to a physiological tempered
nutrient solution and then completely and carefully rinsed through twice in toto with the help of a 10 ml.
syringe with nutrient solution for the removal of the intestinal contents. For the subsequent experiments, two
pieces of intestine of 2 cm. length were separated off and the remaining piece of intestine kept in a
55 refrigerator. The two pieces of intestine were freed in nutrient solution from tissue possibly still attached   55
thereto. Around one end there was applied a sling of silk thread for fixing the piece of intestine in an organ
bath, while around the other end was applied a longer thread with a connecting clamp for fixing to a
recording layer. The piece of organ was thereafter filled with nutrient solution and suspended in a bath vessel
with Carbogen bubbling therethrough and loaded with 0.5 g. After a resting period of 30 minutes, the
60 experiment can commence.   60
There was first plotted a dosage action relationship of the spasmodic. The solution to be tested was
injected by means of a tuberculin syringe with applied single-use canule into the bath liquid. Depending
upon the volume to be injected, for the precise maintenance of the bath content there was previously always
removed an equal volume of nutrient solution. Concentrations were selected which, in geometric steps of a
65 factor of 5, displayed spasmodic effects of > 10% to 100%, the 100% effect being taken as being the limiting   65

concentration, exceeding of which brought about no greater effect. The limiting concentration is taken as reference value and the effects of the lower concentrations were calculated to refer to this 100% value. A complete concentration activity curve was plotted using a piece of intestine.

5   The period of action of the spasmodic on the organ was 5 minutes. Thereafter, the content of the bath vessel was changed three times by rinsing and followed by a resting phase (no addition of substance) of 30 minutes.

The after plotting of the concentration-activity relationship of the spasmodic, the antagonistic strength of action of the substance to be tested was tested. For this purpose, the test substance was injected in a constant concentration into the bath vessel content 3 minutes before application of the spasmodic. The subsequent

10   course of the experiment corresponded to that already described: addition of spasmodic in increasing concentrations, rinsing three times, 30 minute resting phase. Depending upon the effect, the concentrations of the test substance were varied, ten experiments being carried out per concentration.

Analysis and apparatus

15   The experimental apparatus consisted of a horizontally fixed, about 66 cm. long cylinder-shaped glass surround with inlet and outlet taps in which were melt-sealed two pre-heating spirals which were provided on the outside with inlet pipes and each of which open downwardly into a bath vessel of 25 ml. volume closable below by stopcocks. Demineralised water warmed to 34°C. was circulated by an ultrathermostat of the firm "Colora" through the glass surrounded so that the nutrient solution present in the pre-heating

20   spirals and bath vessels was always uniformly warmed. In case of need, it was passed from a higher-standing supply vessel via a tube system into the pre-heating spirals. On the bottom of the bath vessel, for the continuous bubbling through the nutrient solution with Carbogen (95% oxygen and 5% carbon dioxide), there were provided gassing tubes, on the limbs of which, in the lower third thereof, were melt-sealed glass hooks on to which were suspended on one end the previously prepared piece of intestine, whereas the other

25   end was attached with its long thread with a metal recorder lever for MP recordal. Finally, the loading was adjusted on the recorder lever and the star recorder of the lever applied to the MP paper on the recorder drum (diameter 200 mm.) of a kymograph. During the experiment, the MP paper was rolled from the table unrolling device on to the drum. The paper movement was 2.62 mm. $\times$ min^{-1}. The recording breadth could be regulated via an MP generator with incorporated potentiometer. For a better current flow, a contact roller was

30   additionally applied to the MP paper which was connected with the earthing box of the MP generator. After ending of the experiment, the recordings on the MP paper were fixed with a special fixing spray. All apparatus necessary for the recordings were obtained from the firm Braun, Melsungen, Germany.

Evaluation

35   For each concentration in g./ml. there was obtained the arithmetic average values and their standard deviations ($\bar{x}\% \pm s$) of the spasmodic effect.

Results

A 50% spasm was obtained with Carbachol alone (blank experiment) at a concentration of 4.3×10^{-8} g./ml.

40   In the case of the use of the above-mentioned spasmolytically-acting test substances in a concentration of 1.18×10^{-8} g./ml., for the initiation of a 50% spasm, carbachol concentrations of the order of 10^{-6} g./ml. were needed.

In principle, there are three possibilities for the treatment of diseases due to asthma and for bronchial diseases: cortisone or corticosteroids, sympathomimetics and parasympatholytics. As is known,

45   corticosteroids involve serious side effects, for example susceptibility to infections. Sympathomimetics also have considerable symptomatic side effects, for example tachycardia. Parasympatholytics, on the other hand, are characterised by a good measure of success, especially in the case of local administration, by the absence of or only small side effects but, on the other hand, the therapeutic results are not uniform and not certain because of differing response of the symptoms of the disease. In this regard, reference is made to J.F.

50   Keighley, Iatrogenic asthma associated with adrenergic aerosols, Ann. intern. Med., *65*, 985/1966 and F.E. Speizer *et al.*, Observations on recent increase in mortality from asthma, B.M.J., *1*, 335/1968.

It is known that some azoniaspironortropane derivatives possess spasmolytic properties (see Federal Republic of Germany Patent Specification No. 11 94 422 and Arzneimittelforschung, *17*, 714-719/1967. However, these compounds have hitherto only been used in the urogenital region.

55   There is a need for new asthma therapeutics and broncholytics with a parasympatholytic character of action but without a systemic accompanying action, i.e. with effect on the circulatory regulation, and with a dependable action.

It is an object of the present invention to improve the treatment of asthmatic diseases and of diseases of the bronchial region.

60   Thus, the present invention is also concerned with the use of azoniaspironortropanol esters of the general formula (I) as asthma therapeutics and as broncholytics.

In order to confirm the effectiveness of the active materials according to the present invention, inhalative provocations were carried out on awake guinea pigs with a cholinergically-effective aerosol. 3×10^{-7} mole kg^{-1} of active material thereby antagonise an asthmatoid respiratory difficulty brought about by an

65   acetyl-β-methylcholine aerosol 15 minutes after intraperitoneal administration. The therapeutic

effectiveness of the active materials according to the present invention is markedly stronger than that of equimolar dosages of reference substances, such as atropine and isoproterenol.

Method

5

Animal material
animal type: guinea pigs
animal strain: Pirbright white
origin: Lippische Versuchstierzucht Hagemann GmbH & Co., 4923 External 1, Germany
10   sex: male
body weight: about 500 - 700 g.
acclimatisation time: > 8 days

Animal maintenance
15   living space: massive construction, conventional maintenance
room temperature: $22 \pm 2°C$.
atmospheric humidity: 50 - 60% relative humidity
room illumination: artificial 12 hour rhythm
cages: Macrolon lower part and wire mesh covering with feed and water containers; bedding "ssniff" from
20   "ssniff Versuchstierdiäten GmbH, 4770 Soest, Germany
feed: Altromin-MS from Altrogge Spezialfutterwerk, Lage/Lippe, Germany; "ssniff"-MS diet and hay
drinking water: tap water ad libitum
Trospium chloride = MP 194 = 3α-benziloyloxynortropane-8-spiro-1'-pyrrolidinium chloride
dehydrotrospium chloride = WG 71 = 3α-benziloyloxynortropane-8-spiro-1'-(3'-pyrrolinium)chloride
25

Substances, dosages and mode of administration
test substance: trospium chloride (MP 194) (M.W. 428)
dosage: 3×10^{-7} mole ml^{-1} kg^{-1}
mode of administration: intraperitoneally
30   test substance: dehydrotrospium chloride (WG 71) (M.W. 426)
dosage: 3×10^{-7} mole ml^{-1} kg^{-1}
mode of administration: intraperitoneally
reference substance: atropine hydrochloride (Serva; M.W. 325.8)
dosage: 3×10^{-7} mole ml^{-1} kg^{-1}
35   mode of administration: intraperitoneally
reference substance: isoproterenol (Fluka; M.W. 247.72)
dosage: 3×10^{-1} mole ml^{-1} kg^{-1}
mode of administration: intraperitoneally
control substance: physiological saline
40   dosage: 1 ml. kg^{-1}
mode of administration: intraperitoneally
further substances: acetyl-β-methylcholine chloride (Sigma; M.W. 195.7)
concentrations: 0.0316 g. $\times$ 100 ml^{-1} double distilled water
0.0562 g. $\times$ 100 ml^{-1} double distilled water
45   0.1 g. $\times$ 100 ml^{-1} double distilled water
0.178 g. $\times$ 100 ml^{-1} double distilled water
0.316 g. $\times$ 100 ml^{-1} double distilled water
0.562 g. $\times$ 100 ml^{-1} double distilled water
mode of administration: 0.5 ml. min^{-1} by inhalation.
50

Grouping
distribution to the groups: random
animals per group: 10
group division: as far as possible, on one day, animals of the experimental and control groups are taken into
55   the experiment.

Carrying out of the experiments
    The guinea pigs intended for an experiment are, after an acclimatisation time of at least 8 days, subjected twice to an aerosol of 0.1% acetyl-β-methylcholine chloride solution since, as is known from experience,
60   during the first two inhalative provocations, the animals react with more distinct respiratory disturbances than in the case of the subsequent provocations (adaption). If, in the case of the two inhalation phases, a non-sensitivity (absence of respiratory disturbances) is observed towards the exposure, these animals are excluded from the actual experiment.
    For the purpose of aerosol provocation, the guinea pigs are placed individually in an inhalation chamber
65   (see Section 3.6 hereinafter) in which 0.5 ml. of solution per minute are atomised as droplet aerosol by means

of a special nozzle (Rhema, Hofheim, Germany). Dependent upon the active material concentration, as well
as of a pre-treatment possibly carried out, the aerosol exposure leads to a more or less marked dyspnoea, to
attacks of coughing and finally to asphyxia and loss of consciousness following a tonic-clonic cramp of
differeing strength. With the help of a stopwatch, there is recorded the time from the commencement of
5 inhalation to the appearance of the asphyctic state; the animals are immediately removed from the inhalation   5
chamber and, as a rule, recover in a very short period of time (recovery of consciousness and normalisation
of breathing). If, within 180 seconds, no dyspnoea occurs, the inhalation is discontinued.
    In order to demonstrate the protective action of the test and reference substances, the animals in the
experiment, 15 minutes before the commencement of the inhalation, are pre-treated with these substances
10 according to their body weight (control animals correspondingly with isotonic sodium chloride solution) and   10
subjected to logarithmically graduated concentrations of acetyl-β-methylcholine aerosol. One aerosol
concentration is tested per test day; the time between the individual aerosol provocations is at least 1 week.

Analyses and apparatus
15   The inhalation chamber is a Plexiglass container specially made for this purpose, the lid of which can be   15
closed in an air-tight manner by means of rubber sealing and grip closure means. The internal
measurements of the chamber are $285 \times 190 \times 180$ mm., which corresponds to a volume of about 9.75 litres.
The special nozzle (Rhema, Hofheim, Germany, order No. 504104) is fixed to a recess on the lid and ensures a
uniform supply of the available chamber space with the aerosol. The provocation solution is supplied to the
20 nozzle via an infusion pump (Braun, Melsungen, Germany) (0.5 ml./minute) and there atomised with a   20
superpressure of 180 kPa from an attached pressure gas bottle (artificial air, KW-free). For reasons of safety,
the aerosol provocation is carried out under a ventilator.

Evaluation
25   For each of the tested substances (test, reference and control substances) there is taken, in the case of each 25
investigated active material concentration, the percentage proportion of the animals reacting with dyspnoea
for the calculation of the EC_{50}.
    The EC_{50}, as well as the related confidence interval (p >95%), are determined from the probit regression
lines of the percentage values (v. supra) provided with weight coefficients after line adaptation by the
30 "maximum likelihood" method (10 iterations). Furthermore, there is examined the adaption of the lines to   30
the observed data by means of the chiquadrat test. For the evaluation, a calculation programme is
commercially available (Olivetti).

Results
35   The tested substances, trospium chloride as well as dehydrotrospium chloride, show, after intraperitoneal   35
administration, an outstanding broncholytic effect in the case of cholinergically-induced bronchial cramps
on the awake guinea pig. The average effective concentration (EC_{50}) of acetyl-β-methylcholine chloride in the
solution to be atomised is, in the case of the control animals, w = 0.00054 (see the following Table 1). After
pre-treatment with trospium chloride or dehydrotrospium chloride, the corresponding EC_{50} values are w =
40 0.00286 and w = 0.00173, respectively (see the following Tables 2 and 3).   40
    Atropine and isoproterenol were used as reference substances. For atropine and isoproterenol, there were
determined average effective concentrations of the provocation substances of w = 0.00138 and w = 0.00145,
respectively (see the following Tables 4 and 5).
    Furthermore, the average effective concentrations EC_{50} of the provocation substances 15 minutes after
45 intraperitoneal administration of MP 194, WG 71, atropine and isoproterenol are illustrated schematically in 45
Figure 1 of the accompanying drawings.

Table 1

50 Control substance: NaCl (W = 0.009)   50
   mode of administration: intraperitoneal
   dosage: 1 ml kg^{-1}
   active material: acetyl-β-methylcholine chloride
   mode of administration: by aerosol inhalation
55 concentration: see below   55

active material concentration	number of animals		probit analysis	reaction % calculated
	tested	reacting	observed	
60 w				60
0.000316	10	2	20.00	22.79
0.000562	10	5	50.00	52.35
0.000750	10	7	70.00	67.81
0.001000	10	9	90.00	80.64
65 0.001780	10	9	90.00	95.26

65

Test for linearity: $x^2 = 1.2629$ (FG $= 3$)
linearity can be assumed ($\alpha \geq 0.05$)

Result of the probit analysis
5 Average effective concentration of the active material:
  EC_{50}: w $= 0.000539$
confidence interval (P $= 0.95$) : $0.000339 - 0.000855$

Table 2

10
test substance:		trospium chloride	
mode of administration:		intraperitoneal	
dosage:		$3 \times 10^{-7}\,\text{mol ml}^{-1}\,\text{kg}^{-1}$	
active material:		acetyl-β-methylcholine chloride	
mode of administration:		by aerosol inhalation	
concentration:		see below	

active material concentration w	number of animals tested	reacting	probit analysis observed	reaction % calculated
0.000562	10	0	2.50*	5.46
0.001000	10	1	10.00	15.03
0.001780	10	5	50.00	32.00
0.003160	10	5	50.00	53.87
0.005620	10	7	70.00	74.66

* correction according to Bliss
30 test for linearity: $x^2 = 2.0313$ (FG $= 3$)
linearity can be assumed ($\alpha \geq 0.05$)

Result of the probit analysis
average effective concentration of the active material
35 EC_{50}: w $= 0.00286$
confidence interval (P $= 0.95$): $0.00147 - 0.00557$

Table 3

test substance:		dehydrotrospium chloride	
mode of administration:		intraperitoneal	
dosage:		$3 \times 10^{-7}\,\text{mol ml}^{-1}\,\text{kg}^{-1}$	
active material:		acetyl-β-methylcholine chloride	
mode of administration:		by aerosol inhalation	
concentration:		see below	

active material concentration w	number of animals tested	reacting	probit analysis observed	reaction % calculated
0.001000	10	3	30.00	38.74
0.001780	9	6	66.67	50.60
0.003160	10	6	60.00	62.35
0.005620	10	7	70.00	73.08

test for linearity: $x^2 = 1.3234$ (FG $= 2$)
linearity can be assumed ($\alpha \geq 0.05$)

60 *Result of the probit analysis*
average effective concentration of the active material
  EC_{50}: w $= 0.00173$
confidence interval (P $= 0.95$): $0.00031 - 0.00972$

Table 4

reference substance:	atropine chloride
mode of administration:	intraperitoneal
dosage:	$3 \times 10^{-7}\,mol\,ml^{-1}\,kg^{-1}$
active material:	acetyl-β-methylcholine chloride
mode of administration:	by aerosol inhalation
concentration:	see below

active material concentration w	number of animals		probit analysis observed	reaction % calculated
	tested	reacting		
0.000562	10	3	30.00	38.93
0.001000	10	6	60.00	45.98
0.001780	9	5	55.56	53.16
0.003160	10	5	50.00	60.20
0.005620	10	7	70.00	66.95

test for linearity: $x^2 = 1.6245$ (FG = 3)
linearity can be assumed ($\alpha \geq 0.05$)

Result of the probit analysis
average effective concentration of the active material
        EC_{50}: w = 0.00138
confidence interval (P = 0.95): 0.00022 – 0.00888

Table 5

reference substance:	isoproterenol
mode of administration:	intraperitoneal
dosage:	$3 \times 10^{-7}\,mol\,ml^{-1}\,kg^{-1}$
active material:	acetyl-β-methylcholine chloride
mode of administration:	by aerosol inhalation
concentration:	see below

active material concentration w	number of animals		probit analysis observed	reaction % calculated
	tested	reacting		
0.001000	9	3	33.33	36.21
0.001780	8	5	62.50	57.88
0.003160	9	7	77.78	77.28
0.005620	9	8	88.89	90.30

test for linearity: $x^2 = 0.1240$ (FG = 2)
linearity can be assumed ($\alpha \geq 0.05$)

Result of the probit analysis
average effective concentration of the active material
        EC_{50}: w = 0.00145
confidence interval (P = 0.95): 0.00050 – 0.00426

Assessment
    The test substances trospium chloride and dehydrotrospium chloride are, 15 minutes after intraperitoneal administration, comparable with or superior to the well known parasympatholytics atropine and the β-sympathomimetic isoproterenol with regard to their broncholytic effectiveness (see Figure 1 of the accompanying drawings). From the calculations of the concentrations of acetyl-β-methylcholine chloride which, in each case, are on average effective, which is necessary for the inhalation of a dyspnoea, there can be ascertained a greater effectiveness of the test substances, especially of trospium chloride, in comparison with the reference substances.
    In order to test the receptor specificity of the compounds according to the present invention, the specificity of the cholinergic antagonisation must be demonstrated. A model for this is the measurement of the

anticholinergic effectiveness on isolated tracheal spirals of the guinea pig.

The test substance used was 3α-benziloyloxynortropane-8-spiro-1'-pyrrolidinium chloride (trospium chloride; MP 194), ipratropium bromide being used as comparison substance.

5 1. *Summary*   5
MP 194 is competitively antagonistically effective on the isolated tracheal spirals of the guinea pig in comparison with acetyl-β-methylcholine chloride. Its strength of activity is thereby equivalent to the reference substance ipratropium bromide but, depending upon the mode of administration and upon the dosage (see Rote Liste, 1985, No. 09015), the usual side effects of ipratropium bromide are considerably
10 reduced or do not occur at all.   10

2. *Interrogatory*
There is to be determined the anticholinergic effectiveness of MP 194 in comparison with the reference substance ipratropium bromide on the isolated tracheal spirals of the guinea pig.

15   15
3. *Method*
3.1 Animal material
3.1.1. animal species: guinea pig
3.1.2. animal strain: Pirbright white
20 3.1.3. origin: Hagemann GmbH & Co., 4923 Extertal 1, Germany   20
3.1.4. sex: male
3.1.5. body weight: about 500 g.
3.1.6. acclimatisation time: > 8 days
3.2. Animal maintenance
25 3.2.1. living space: massive construction, conventional maintenance   25
3.2.2. room temperature: 22 ± 2°C.
3.2.3. relative atmospheric humidity: 50 ± 15%
3.2.4. room illumination: artificial dark/light rhythm in 12 hour intervals
3.2.5. animal cages: Makrolon lower part and wire mesh covering with feed and water containers; bedding
30 "ssniff" (Versuchstierdiäten GmbH, 4770 Soest, Germany)   30
3.2.6. feed: "ssniff" guinea pig diet
3.2.7. drinking water: tap water ad libitum
3.3. Substances, dosaging and mode of administration
3.3.1. test substance (test antagonist)
35 trospium chloride (MP 194) (M.W. 428)   35
solvent: tyrode solution
bath concentrations: 1×10^{-9} M/ml. bath solution
3.16×10^{-9} M/ml. bath solution
1×10^{-8} M/ml. bath solution
40   1×10^{-7} M/ml. bath solution   40
administration volume: 50 μl./28 ml. bath solution
3.3.2. reference substance (reference antagonist)
ipratropium bromide (Atrovent) (M.W. 412.4)
solvent: tyrode solution
45 bath concentrations: 1×10^{-9} M/ml. bath solution   45
3.16×10^{-9} M/ml. bath solution
1×10^{-8} M/ml. bath solution
1×10^{-7} M/ml. bath solution
administration volume: 50 μl./28 ml. bath solution.
50 3.3.3. further substances (reference antagonists)   50
3.3.3.1. acetyl-β-methylcholine chloride (Sigma) (M.W. 195.7)
solvent: tyrode solution
bath concentrations: 1×10^{-7} M/ml. bath solution
1×10^{-6} M/ml. bath solution
55   1×10^{-5} M/ml. bath solution   55
1×10^{-4} M/ml. bath solution
1×10^{-3} M/ml. bath solution
1×10^{-2} M/ml. bath solution
3.16×10^{-2} M/ml. bath solution
60 administration volume: 50μl./28 ml. bath solution, cumulative   60
3.3.3.2. tyrode solution as nutrient medium

component	mMole/1.	stock solution	ml. stock solution/ litre tyrode solution
NaCl	139.2	58.00 g/l (1 M)	139.2 ml.
KCl	2.7	74.56 g/l (1 M)	2.7 ml.
$CaCl_2.2H_2O$	1.8	147.00 g/l (1 M)	1.8 ml.
$MgCl_2.6H_2O$	0.245	99.62 g/l (0.49 M)	0.49 ml.
$NaHCO_3$	11.9	21.00 g/l (0.25 M)	47.6 ml.
$NaH_2PO_4.H_2O$	0.4	4.00 g/l (0.03 M)	15.6 ml.
$C_6H_{12}O_6$	5.5	-	1.0 g.

double distilled water ad 1000 ml.

Calcium chloride is hydroscopic. Therefore, the stock solution must be titrated with the help of a Chlor-o-Counter (Marius-Chlor-o-Counter, Kipp and Zonen, 6242 Schönberg/Taunus, Germany).

In the mixing of the various stock solutions, it is to be noted that calcium precipitates out with bicarbonate and phosphate when the solutions are mixed together in high concentration. This is avoided by first diluting the 1.8 ml. of calcium chloride parent solution with about 100 ml. of double distilled water, the other stock solutions in a measurement flask already having been substantially made up with double distilled water and only then adding the calcium solution.

3.4. Grouping
3.4.1. division into groups: random

3.4.2. number of preparations:

of the test substance group: n = 4 $(1 \times 10^{-9}M)$
n = 2 $(3.16 \times 10^{-9}M)$
n = 2 $(1 \times 10^{-8}M)$
n = 4 $(1 \times 10^{-7}M)$

of the reference substance group:
n = 4 $(1 \times 10^{-9}M)$
n = 2 $(3.16 \times 10^{-9}M)$
n = 2 $(1 \times 10^{-8}M)$
n = 4 $(1 \times 10^{-7}M)$.

3.5. Carrying out of the experiments
The guinea pig is stunned by a blow on the neck. Subsequently, the whole of the trachea is roughly freed beginning from the larynx up the tracheal bifurcation, removed and transferred to tempered (37°C.) and carbogenised tyrode solution. After surrounding connective tissue has been removed as far as possible, the preparation is cut up spirally by means of fine scissors at an angle of about 45° and separated into two equal sized sections. After weighing, both preparations are provided proximally and distally with a silk thread. One thread serves for fixing the preparation by means of a loop to the bottom of the bath and the other is connected via a hook with the transducer above the bath vessel.

Subsequently, the preparations, corresponding to the calibration, are prestressed with about 80 mN and equilibrated from 50 – 100 minutes. During the equilibration phase, the nutrient solution in the bath vessels is renewed in 15 minute intervals. As soon as the resting muscle tonus of the preparation has stabilised, there takes place the cumulative addition of the agonist, whereby the addition of the next highest concentration first takes place when no further increase of contraction is recognisable (plateau). When the maximum contraction height of the preparation is achieved, the cumulative agonist addition is ended and the preparation is rinsed. After a further equilibration phase (v. supra), the cumulative addition of the agonist is repeated but this time in the presence of the test or reference antagonist.

3.6 Analyses and apparatus
3.6.1. The perfusion part consists of an L-shaped organ bath in the hollow space of which (longer limb) runs a double glass spiral through which the nutrient solution is passed into the actual bath vessel (28 ml. content; shorter limb). This bath vessel is divided into two chambers which are, however, connected together by two transverse connections. Thus, the supply of the organ with Carbogen (95% oxygen and 5% carbon dioxide) can take place indirectly from the smaller rearmost of the two chambers, whereby the organ does not hang directly in the Carbogen inflow which, inter alia, makes possible a more precise recordal of the organ reactions. The inlet chambers as well as the feeding glass spirals are tempered from the outside to 37°C. by a separate liquid circulation. This tempering takes place with the help of a "Colora" ultra-thermostat type K (Colora Messtechnik GmbH, Dusseldorf, Germany) which serves as thermostat and pump. In order, in case of need, always to have available ready-for-use nutrient solution, above the organ bath is provided a double-walled storage container in which the nutrient solution is also tempered and carbogenised. This is connected via a glass stopcock and a polypropylene tube with double glass spiral in the interior of the organ bath.

3.6.2. The measurement and recording part includes a transducer (Statham-Universal-Zelle UC-2; Hugo Sachs Elektronic KG, Hugstetten, Germany). By means of a hanging-in weight, a force of 40 mN is produced on the transducer which passes as electrical signal via a connecting cable to a bridge amplifier. The amplification is smoothly so regulated that the force provided corresponds to a constant value on the scale or
5 an analogous value on the millimeter paper of the recorder (dependent upon the amplification; see below). After fixing the organ, the preparation is prestressed to the double mark, corresponding to 80 mN. The recorder connected with the amplifier (Hellige, Freiburg/Breisgau, Germany) records all analogue signals on thermosensitive paper with millimeter divisions. The recorder amplification is thereby so regulated that the pulling force of the weight (40 mN) on the transducer corresponds to an indicator stroke of 4 cm. (calibration:
10 force produced by means of the weight $\triangleq$ 4 cm. on the analogue protocol).

3.7 *Evaluation*
    The cumulative addition of the agonist leads on the isolated tracheal spiral to a dosage-dependent contraction force increase which is recorded proportionally on the analogue recorder (see calibration). From
15 these analogue protocols is carried out the quantitative evaluation of the cumulative dosage action curves according to the method of van Rossum (Cumulative dose-response curves. II. Technique for the making of sode-response curves in isolated organs and the evaluation of drug parameters, Arch. int. Pharmacodyn., *143*, 299-330/1963). For this purpose, the absolute measurement data (in [mm]) is first converted on the basis of the maximum effect (E_{Am} or E_{AmB}), which is taken as being 100%, into percentage values. By means of
20 non-linear regression, from these data there is determined for each individual preparation the ratio of the molar concentrations of the agonists (quotient = x) which are necessary in order precisely to achieve half of the maximum effect in the presence and absence of the test or reference antagonists of the molar concentration [B] ($-\log$ [B] = pA_x). On the basis of the formula $pA_2 = pA_x + \log (x-1)$ (see H.O. Schild, pA, a new scale for measurement of drug antagonism, Brit.J.Pharmacol., *2*, 189/1947; E.J. Ariens and J.M. van
25 Rossum, pDx, pAx and pDx values in the analysis of pharmacodynamics, Arch.int.Pharmacodyn., *110*, 275-300/1957), there is determined the negative decadic logarithm of the molar antagonist concentration (pA_2) in the case of which x corresponds to the value of 2, i.e. in the case of the presence of antagonists in the appropriate molar concentration, the molar agonist concentration must be doubled in order to achieve the same effect as without the action of the antagonists. The quality of the antagonism
30 (competitive/non-competitive) is tested statistically on the basis of the comparison of the maximum effect in the absence (E_{Am}) and presence (E_{AmB}) of the test or reference antagonists. (t-test with paired arrangement). Finally, the difference of the $pA_2 \pm$ s between test and reference antagonist is examined for significance (t-test of two independent samples).

35 4. *Results*
    MP 194 and ipratropium bromide (Atrovent) show on isolated tracheal spirals from the guinea pig a comparable, dosage-dependent antagonism against the cholinergic agonist acetyl-β-methylcholine chloride (see Figure 2 of the accompanying drawings). The $pA_2 \pm$ s determined for MP 194 of 9.26 ± 0.29 does not differ significantly from the $pA_2 \pm$ s for ipratropium bromide of 9.31 ± 0.39 (see Table 1).
40   The quality of the antagonism is competitive not only the case of MP 194 but also in the case of ipratropium bromide, on the basis of the comparison between the maximum effects in the case of the absence and presence of the antagonist in question (see the following Table 6).

5. *Assessment*
45   The investigation demonstrates the clear anticholinergic effectiveness of MP 194 on isolated tracheal spirals from the guinea pig and thus supplements the earlier investigations of effectiveness on the awake animal. The better quantification of the results of the in vitro models also permits the conclusion that MP 194 is, with regard to the strength of action, equal to the reference substance ipratropium bromide (see the pA_2 values). Furthermore, on the basis of the investigation, a competitive antagonism of both substances can be
50 assumed (see E_{AmB}/E_{Am}).

Table 6

	MP 194	ipratropium bromide
$pA_2 \pm$ s	9.26 ± 0.29	9.31 ± 0.39
$E_{AmB}/E_{Am} \pm$ s	1.09 ± 0.22	1.10 ± 0.24

CLAIMS

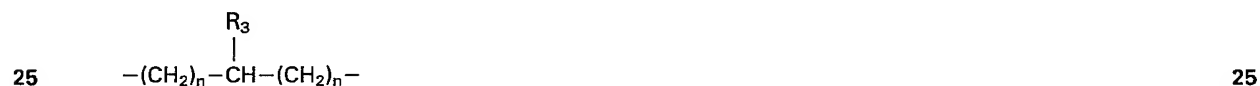1.   Process for the preparation of azoniaspironortropanol esters of the general formula:-

5

10   (I)

15
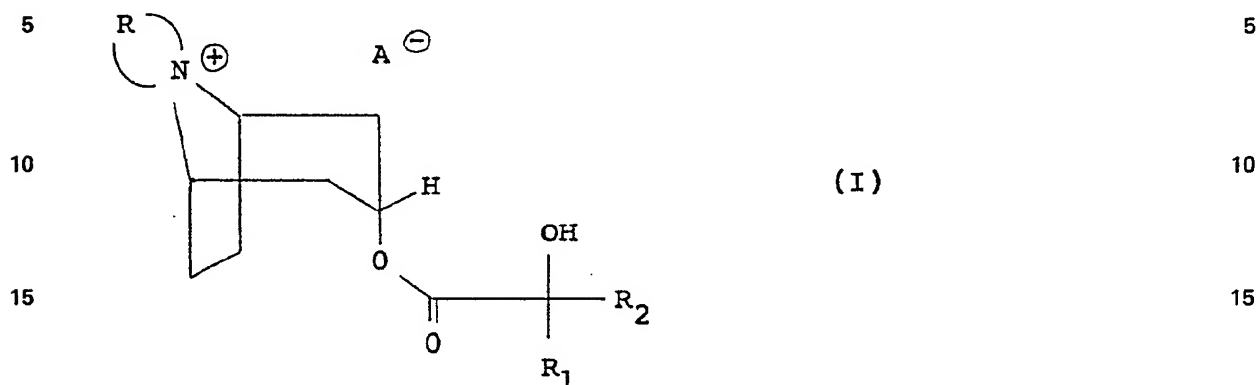
20 wherein R signifies one of the following radicals:
    a) an alkylene radical of the general formula:-

$$R_3$$
$$-(CH_2)_n-CH-(CH_2)_n-$$
25

in which R_3 is a hydrogen atom or an alkyl, benzyl, aryl or alkoxy carbonyl radical and n is a whole number of from 1 to 4,
    b) an alkenylene radical of the general formula:-

30

$$R_4 \qquad R_5$$
$$C = C$$
35
$$-(CH_2)_n \qquad (CH_2)_n-$$

in which R_4 and R_5, which can be the same or different, are hydrogen atoms or alkyl or alkenyl radicals and n is a whole number of from 1 to 4,
40   c) an azaalkylene radical of the general formula:-

$$R_6$$
$$-(CH_2)_n-N-(CH_2)_n-$$
45

in which R_6 is a hydrogen atom or an alkyl, alkoxycarbonyl or acyl radical and n is a whole number of from 2 to 4,
    d) an oxaalkylene radical of the general formula:-

50      $$-(CH_2)_n-O-(CH_2)_n-$$

in which n is a whole number of from 2 to 4,
    e) an epoxyalkylene radical of the formula:-

55      $$-CH_2 - CH - CH - CH_2-$$
$$\diagdown \diagup$$
$$O$$
    f) an o-phenylene radical of the general formula:-

(chemical structure)

g) a peri-naphthylene radical of the general formula:-

(chemical structure)

or

h) a 2,3-quinoxalinene radical of the general formula:-

(chemical structure)
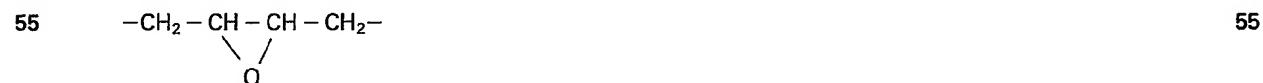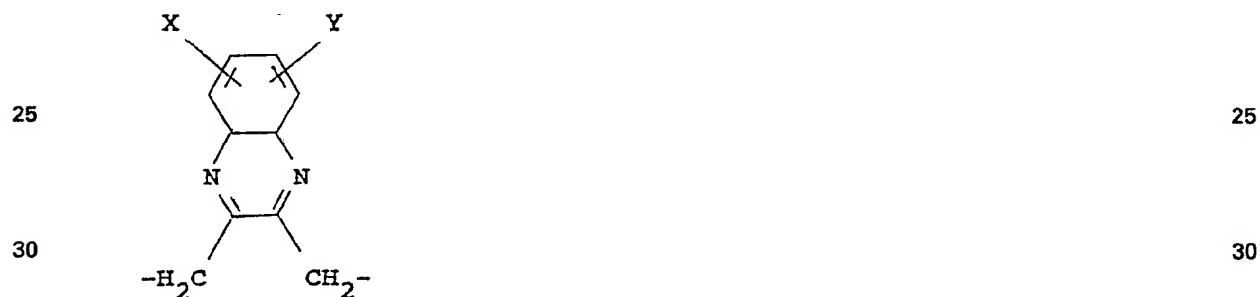
in which in formulae f) to h), the symbols X and Y, which can be the same or different, are hydrogen atoms or
alkyl or alkoxy radicals;
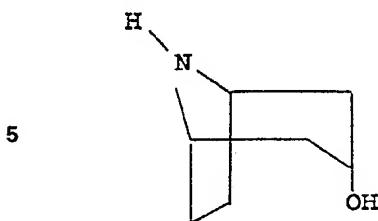and wherein R_1 and R_2, which can be the same or different, are hydrogen or halogen atoms or alkyl, alkoxy,
alkoyl, cyclohexyl, phenyl, alkylphenyl, alkoxyphenyl, halophenyl, thienyl or furyl radicals, the alkyl moieties
in the said radicals containing up to 6 carbon atoms and being straight-chained or branched, and $A^{\ominus}$ is the
anion of a mono- to tribasic mineral acid, by
a) demethylation of tropine to give nortropine,
b) reaction of nortropine with a dihalide to give a corresponding azonia compound, and
c) esterification of the azonia compound, wherein A)
the demethylation of tropine of the formula:

(chemical structure)

(II)

is carried out either by working in a C_1-C_3-chloroalkane which contains at least one trichloromethyl radical in
the presence of an oxidation agent in basic aqueous solution or the tropine is reacted with a chloroformic
acid ester in an inert solvent in the presence of an acid-binding agent to give an 8-alkoxycarbonylnortropine
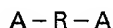and this is hydrolysed with a base in aqueous solution,
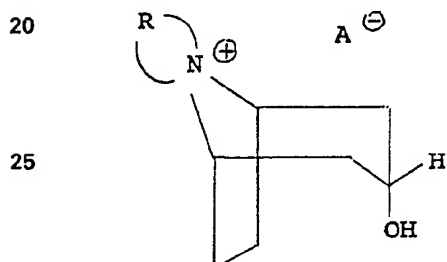B) the nortropine thus obtained of the formula:-

(III)

is reacted at ambient temperature for 1 or more days in a dipolar aprotic solvent with a compound of the general formula:-

$$A - R - A$$

in which A and R have the above-given meanings, in the presence of a secondary or tertiary amine and
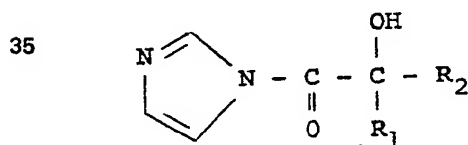C) the compound thus obtained of the general formula:-

(IV)

in which R and $A^\ominus$ have the above-given meanings, is esterified in an anhydrous, dipolar, aprotic solvent with an imidazolide of the general formula:-

(V)

in which R_1 and R_2 have the above-given meanings, in the presence of a catalyst, and
D) when the radical R contains one or more olefinic double bonds in the azonium ring after passing through steps B andor C, this unsaturated compound is optionally hydrogenated in a polar solvent with the help of a noble metal catalyst to give the corresponding saturated compound of general formula (I) in which R is a radical a) as defined hereinbefore.

2. Process according to claim 1, wherein in the first variant of step A, the demethylation is carried out with potassium ferricyanide, chloroform and sodium hydroxide.

3. Process according to claim 1 or 2, wherein in the first variant of step A, there is used a 1 to 5 fold molar amount of chloroalkane, referred to the tropine.

4. Process according to any of the preceding claims, wherein the reaction temperature in the first variant of step A is from 20 to 30°C.

5. Process according to claim 1, wherein, in the second variant of step A, the reaction is carried out in chloroform in the presence of an alkali metal hydrogen carbonate.

6. Process according to any of the preceding claims, wherein in step B the ratio of nortropine:amine:dihalide is 1:2:4.

7. Process according to any of the preceding claims, wherein the amine used in step B is diethylamine.

8. Process according to any of the preceding claims, wherein the catalyst used in step C is 4-(N,N-dimethylamino)-pyridine.
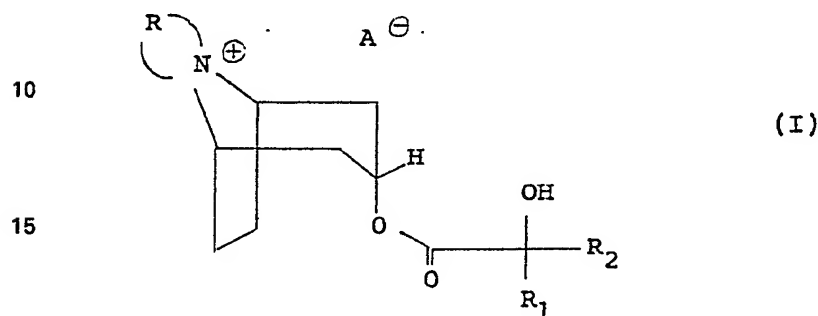
9. Process according to any of the preceding claims, wherein the dipolar aprotic solvent used in step C is acetonitrile.

10. Process according to any of the preceding claims, wherein the dipolar aprotic solvent used in step B is dimethylformamide and/or acetonitrile and/or chloroform.

11. Process according to any of the preceding claims, wherein in step D the hydrogenation is carried out in water or in an alcohol containing up to 4 carbon atoms in the presence of platinum dioxide or palladium on active charcoal.

12.   Process according to claim 11, wherein the alcohol used is methanol.

13.   Process according to claim 1 for the preparation of azoniaspironortropanol esters, substantially as hereinbefore described and exemplified.

14.   Azoniaspironortropanol esters, whenever prepared by the process according to any of claims 1 to 13.

15.   Azoniaspironortropanol esters of the general formula:-

(I)

wherein R, R_1, R_2 and $A^\ominus$ have the same meanings as in claim 1, but excluding the following compounds:
azoniaspiro-[3α-phenylglycoloyloxynortropan-8,1'-pyrrolidine] chloride,
azoniaspiro-[3α-diphenylglycoloyloxynortropan-8,1'-pyrrolidine] chloride,
3α-phenylglycoloyloxynortropan-8-spiroisoindolinium chloride,
3α-diphenylglycoloyloxynortropan-8-spiroisoindolinium chloride,
3α-phenylglycoloyloxynortropan-8-spiro-4'-morpholinium chloride,
3α-diphenylglycoloyloxynortropan-8-spiro-4'-morpholinium chloride,
azoniaspiro-[3α-cyclohexylphenylglycoloylnortropan-8,1'-pyrrolidine] chloride,
azoniaspiro-[3α-phenylglycoloyloxynortropan-8,1'-piperidine] chloride and
azoniaspiro-[3α-diphenylglycoloyloxynortropan-8,1'-piperidine] chloride.

16.   Azoniaspironortropanol esters according to claim 15 which are hereinbefore specifically exemplified.

17.   Pharmaceutical compositions containing at least one compound according to claim 15 or 16 in admixture with conventional pharmaceutical carriers and/or additives.

18.   The use of compounds of general formula (I) given in claim 1 as a broncholytics or for the treatment of asthma.

a) demethylation of tropine to give nortropine,

b) reaction of nortropine with a dihalide to give a corresponding azonia compound, and

c) esterification of the azonia with an aryl imidazolide compound, using specified conditions in each step.